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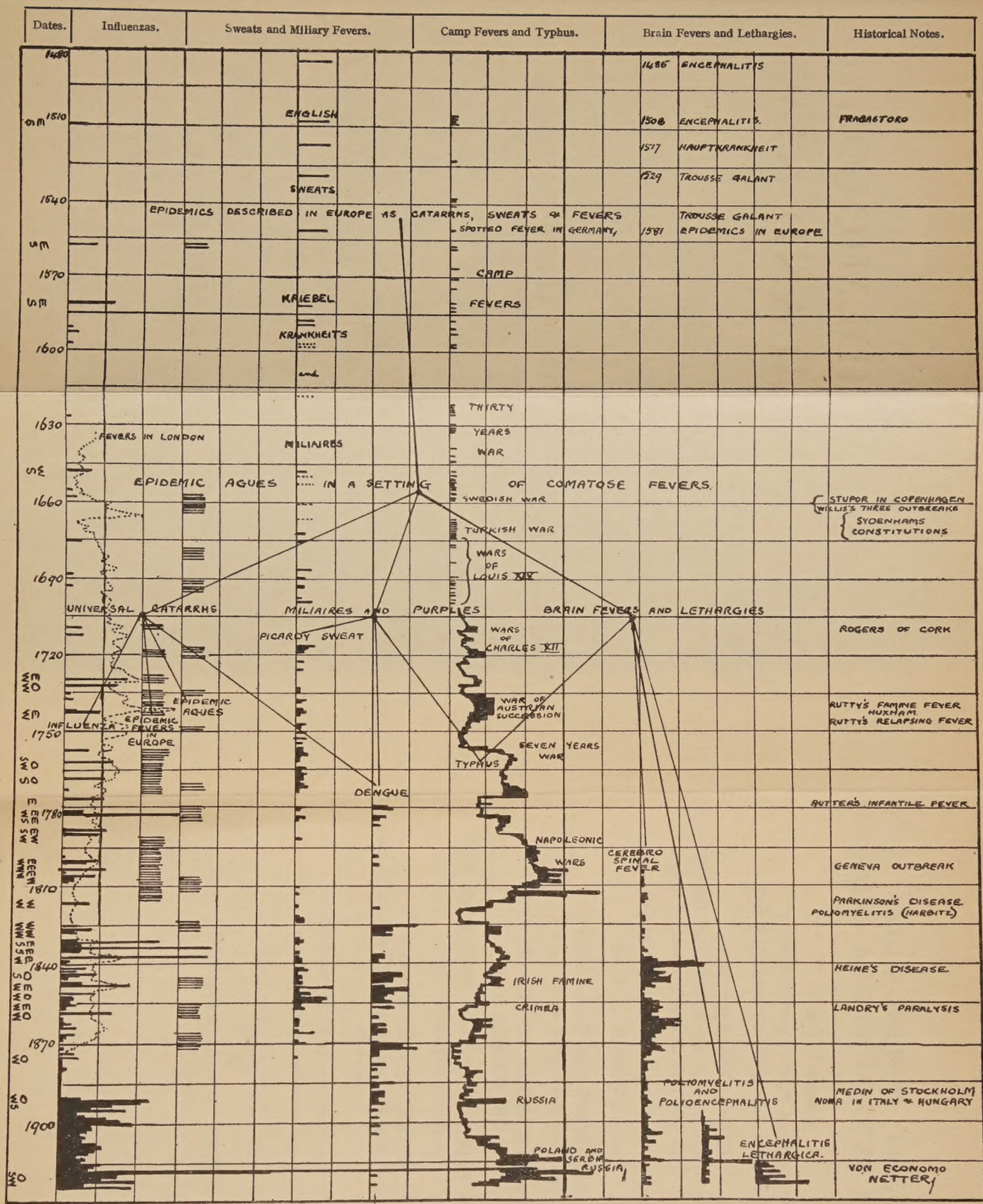

EVOLUTIONARY DEVELOPMENT OF THE INFLUENZAL CONSTITUTION.

The letters W and S in the extreme left hand margin stand for Winter and Summer respectively.

The letters O E and W in the adjoining column stand, O for world-wide Influenzas, and E and W stand for Influenzas of which accounts are forthcoming from the Eastern and Western Hemispheres only.

[*Frontispiece*

EPIDEMIOLOGY OLD AND NEW

BY

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1929

Non fingendum, aut excogitandum, sed inveniendum, quid Natura faciat aut ferat.—BACON.

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CONTENTS

		PAGE
	AUTHOR'S NOTE	ix
	PROLEGOMENA	1
I	INFLUENZA, 1915-1925	32
II	EPIDEMICS IN LONDON IN THE TIME OF SYDENHAM AND AT THE PRESENT DAY *Some Contrasts and Some Resemblances.*	69
III	THE HISTORY OF EPIDEMIOLOGY DURING THE LAST HUNDRED YEARS (*i.*) *The Germ Theory and the Old Epidemiology*	103
IV	THE HISTORY OF EPIDEMIOLOGY DURING THE LAST HUNDRED YEARS (*ii.*) *The Return to the Hippocratic Method*	131
	IN RETROSPECT	163
	REFERENCES	175

77577

ILLUSTRATIONS

PAGE

Evolutionary Development of the Influenzal Constitution *Frontispiece*

Types to which the Measles and Influenza Waves Conform 11

Mortality in London (1890-1923) from Influenza, Bronchitis, Pneumonia and Diseases of the Circulatory System—and Mean Temperature (Greenwich) 26

Diagram illustrating Certain Aspects of the Relationship Between Cerebro-Spinal Fever and Influenza 40

Influenza in London in Relation to Epidemic Diseases of the Central Nervous System 57

Typhoid Fever and Influenza in London 67

London Annual Deaths (1841-1924) 71

"Setting" of Influenzas on the Crests of Waves of Fevers as seen in the London Bills of Mortality 138

London Death-Rates in Registration Times illustrating the Appearances of Influenza on the Crests of Waves of Fevers 149

The Mortality Among Men of Genius from Influenza 152

AUTHOR'S NOTE

This book represents an attempt to make comparison between the behaviour of epidemics, as seen in and from London during the last forty years, and the corresponding happenings in Sydenham's Time. Dr. Joseph Frank Payne, in the final sentence of his "Thomas Sydenham", in the "Masters of Medicine" series, observed: 'It is only by considering his life as a whole, from his youth upwards, that we can understand the complex influences, intellectual, political, and religious, which helped to mould the character of the great Puritan physician, Thomas Sydenham'. So, too, it is only by considering his work as a whole, from his first piece, of 1666, to his two latest writings (both of which have the motto quoted on page iv. prefixed to them), that we can fully appreciate all he accomplished—not by imagining, or thinking out, but by finding out, what Nature does or produces, in connexion with epidemic diseases.

During the last thirty-five years Creighton's great "History of Epidemics in Britain" has been largely instrumental in bringing about a return to the Hippocratic method practised by Sydenham, that of studying the natural history of disease. The preceding half century had been mainly devoted to opening up the new world of microscopic life and to development of the germ-theory; while, more recently, the deeper abysses of the

ultra-microscopic have been tentatively explored. The macroscopic, however, cannot be wholly lost sight of, and so relativists and cosmogonists are beginning to lift up their heads again; even epidemiology shows signs of reviving in the sunshine of a new "climate of opinion".

Sydenham advised any one desiring "to fish out the species of a continued fever", to "choose for his field of observation some large and populous place". The present enterprise was accordingly inaugurated by making comparison between the epidemics of London to-day and those of Sydenham's time. A recent invitation, to deliver two Chadwick Lectures, led to close study of the history of epidemiology during the last hundred years. At this stage, Dr. F. G. Crookshank suggested a complete discussion of results under the title "Epidemiology, Old and New". The author has endeavoured faithfully to carry out the scheme thus outlined by Dr. Crookshank, and desires to record his deep indebtedness to him, for help and guidance.

PROLEGOMENA

IN the Lowell Lectures, delivered in Boston in 1926, on *Religion in the Making*, Professor Whitehead (64a) pointed out that history presupposes a metaphysic. He added, " It is a curious delusion that the rock upon which our beliefs can be founded is an historical investigation. You can only interpret the past in terms of the present. The present is all that you have ; and unless in this present you can find the general principles which interpret the present as including a representation of the whole community of existents, you cannot move a step beyond your own little patch of immediacy." Active interest in the epidemiological scene presented in London during the last forty years has left the present writer little leisure for finding general principles, which will interpret it (speaking epidemiologically) as " including a representation of the whole community of existents " ; but he is emboldened to describe his experiences by the saying of Sydenham, quoted in the preceding Note. Furthermore, study of Sydenham with application to his writings of such general principles as have chanced to emerge to view, here and now, does lead to the definite conclusion (despite the amount of water which has flowed under London Bridge in the last 250 years) that fishing out the species of fevers in the years following 1915 yields

results presenting such striking correspondences, with those obtained in the years following 1673, as forcibly to call to mind Francis Galton's identical twins, who resembled one another so closely that each of them was more like his brother than himself.

Sydenham's advice, in point of fact, directs attention to a general principle of fundamental importance in epidemiology—namely, that due weight must be given to the macroscopic—at least it must not be entirely set aside in favour of the microscopic—point of view. This general principle seems to be winning some measure of recognition now in fields other than those concerned with study of epidemic diseases; but, be this as it may, there can be no question concerning the appropriateness of its application in epidemiology.

Then there is another general principle to be borne in mind. The Hippocratic method, so Creighton told us, always took account of "gradations, modifications, affinities," between diseases, as well as of differences. The germ theory, when it carried everything before it, in the "eighties," swept epidemiology off its feet and it was some time before the importance of *soil* (as well as of *seed*) again became fully recognised; even then to allude to the possible influence of a "tertium quid" was felt to be in bad taste.

However, Longstaff (36) worked out the remarkable relationships, as regards periodicity of occurrence, of the various members of the scarlet fever group of diseases, and noted their common tendency to prevail more particularly in years with deficiency of rainfall. Again,

Pettenkofer in Munich declared that, in addition to *x* and *y* (the seed and the soil of the "contagionists"), there was a "*z*" to be reckoned with, and he thus founded the school of "localists." Several papers were read, moreover, at the Epidemiological Society's meetings in the latter half of the nineteenth century, on the relations between scarlet fever and diphtheria; and the curious association, specially discussed by Murchison (39) and by T. W. Thompson (59), between typhus and relapsing fevers, was again and again brought under scrutiny. When cholera appeared in the "nineties" no one at first seems to have recollected the belief, which had some vogue in earlier prevalences of cholera, that it tended to manifest itself in association with influenza. In 1893, however, Bulstrode's report (5a) on the outbreak of diarrhœa in the Greenwich Infirmary made it evident that this particular prevalence, one of gastro-intestinal influenza, only just missed being diagnosed as cholera; in many instances, similar risk of like confusion was encountered in those early "nineties," when cholera and influenza were both rife in Europe.

Furthermore, the tendency to class gastro-intestinal prevalences by reference to the "causal organisms" associated with them, and to ignore the possibility of the relation of any of these outbreaks to influenza, was conspicuously apparent at this time. Water and milk and various kinds of food (ice-cream, celery, water-cress, etc.) were not unnaturally, as it was then thought, appealed to when grouped cases of fever, diarrhœa, etc., occurred. A flood of light was, however, thrown on epidemic

prevalences in which there was a *prima facie* case against water or food, when the spread of typhoid fever and cholera by shell-fish was at length clearly established. Bulstrode's great report (5c) on the Winchester and Southampton mayoral-banquet outbreaks opened up a new chapter in epidemiology; and his detailed survey (5b) of the shell-fish layings round the coast led the way in effecting the great reduction in typhoid mortality which thereupon followed. In London, moreover, in 1900, a considerable prevalence of typhoid fever simultaneously affecting areas in three somewhat widely separated boroughs, was shown to be due to small plaice, at that time not infrequently consumed in an ungutted state, as it then transpired, by very poor people. In the London Annual Reports for that and several succeeding years (25a), and in Presidential Addresses to London Medical Officers of Health (25b), the question of water, shell-fish and ungutted fish, in relation to typhoid fever and cholera epidemics, was submitted to detailed examination.

An alternative to the water and food origin of cholera and typhoid fever was forthcoming early in the present century, when the healthy carrier hypothesis was formulated. Koch, finding that direct spread from case to case in cholera and typhoid fever could not possibly be held, at any rate in the vast majority of instances, to explain the occurrence of infection, and discovering also, that the cholera vibrio and the typhoid bacillus were very frequently demonstrable in persons showing no symptoms of illness, suggested that "healthy carriers" of

the organisms in question were sometimes, indeed, he thought perhaps usually, the cause of spread of those diseases. The great campaign in S.W. Germany was accordingly inaugurated. The inadequacy of Koch's thesis to explain the typhoid fever of London was pointed out in papers read before the Epidemiological Section of the Royal Society of Medicine (25c, d, e) and also in the two Presidental Addresses already referred to.

With establishment of a school medical service in London systematised efforts were made to control the spread of diphtheria ; school closure was at first habitually employed, but after a time reliance came to be placed mainly upon excluding particular scholars, and, in some instances, apparently healthy children, swabs from whose throats were found to contain bacilli morphologically indistinguishable from diphtheria bacilli, were kept out of school for weeks or even months. Experience, however, showed the impracticability of carrying out such " exclusions of particular scholars," unless careful regard were paid to the circumstances at the school as well as to the laboratory results, i.e., to the epidemiological as well as the bacteriological considerations. The importance of attaching due weight to the previous history of the school, and to the clinical appearances on examination of the children's throats, was especially realised in connection with prevalence of throat-malady at an industrial school in South London. Prolonged observation was there made of two children, who had been thought of as possible disseminators of infection, and the facts elicited were set out in detail in the London Annual Report for 1915

(25i, 1). From that time onwards, more and more reliance came to be placed upon close study of clinical appearances in association with the corresponding laboratory reports and, after some years' experience had been gained, the method was commended as a practical solution of the problem by the Ministry of Health. (Reports on Public Health, etc. No. 10, 1921, p. 7.) A like difficulty arose in connection with cerebro-spinal fever in 1915, and here, again, the importance of considering the epidemiological aspect in each particular case in conjunction with the bacteriological results, became insistently apparent.

While administrative difficulties associated with control of healthy carriers were thus forced upon attention, it was at the same time becoming increasingly realised that measures taken, for improving water supplies and preventing the sale of estuarially polluted shellfish and fish, were being followed by cessation or marked reduction of prevalence of cholera and typhoid fever. The mortality from epidemic throat maladies had greatly declined, but the extent to which prevalence was still maintained prompted further enquiry regarding the "obscure factors," the possible existence of which had, some forty years before, been suspected by Mr. T. W. Thompson. The close relationships between diphtheria and scarlet fever had long been recognised; "return cases" focussed renewed attention upon this question. The enquiries made in London suggested that the flea acted as an intermediary, spreading infection from child to child, and the outcome of study of the points of interest thereupon

arising, was fully summarised in the London Annual Report for 1917 pp. 35-37. In the same report (p. 8) appeared a discussion of the as yet incompletely explored relationships between influenza and the prevalences associated with it.

Meantime great interest had been aroused in research laboratories by the discovery of de Schweinitz, that the germ of hog-cholera was a " filter-passer " and that the hog-cholera bacillus was thus merely an " associated " and not a " causal " organism ; this discovery greatly stimulated enquiry with regard to ultravisible viruses ; and soon after this the subject of " mutation of bacilli " began to arouse interest. These laboratory researches greatly facilitated administrative work, inasmuch as they made it clear that there had been a tendency, in the preceding ten or fifteen years, to stress unduly the importance of waging war upon organisms, which might after all prove to be mere " associated organisms " not possessed of primary " causal " significance. It may be added that the relationships of the " ultravisible viruses " to public health work came under consideration in a paper read before the Royal Society of Medicine (25f, 2) ; and some of the administrative difficulties of earlier years were referred to in an address on " Sympathetic Magic and the Public Health " read at the Sanitary Institute Congress in 1923 (25g).

It was in an atmosphere charged with such positive and negative electricities that the present writer's apprenticeship in the study of epidemics in London commenced and was carried on. In succeeding chapters special

consideration is devoted to the influenzal family of fevers. Attention was necessarily largely directed to influenza and its associates; for the first half of the apprenticeship included the years of the great prevalences of the "nineties"; moreover, these were the years in which Creighton's *History of Epidemics in Britain* appeared. It thus chanced that during this period "influenza was in the air," being actually present in London in epidemic form, and much discussed owing to the appearance in 1891-94 of the classical work dealing with its records in times past.

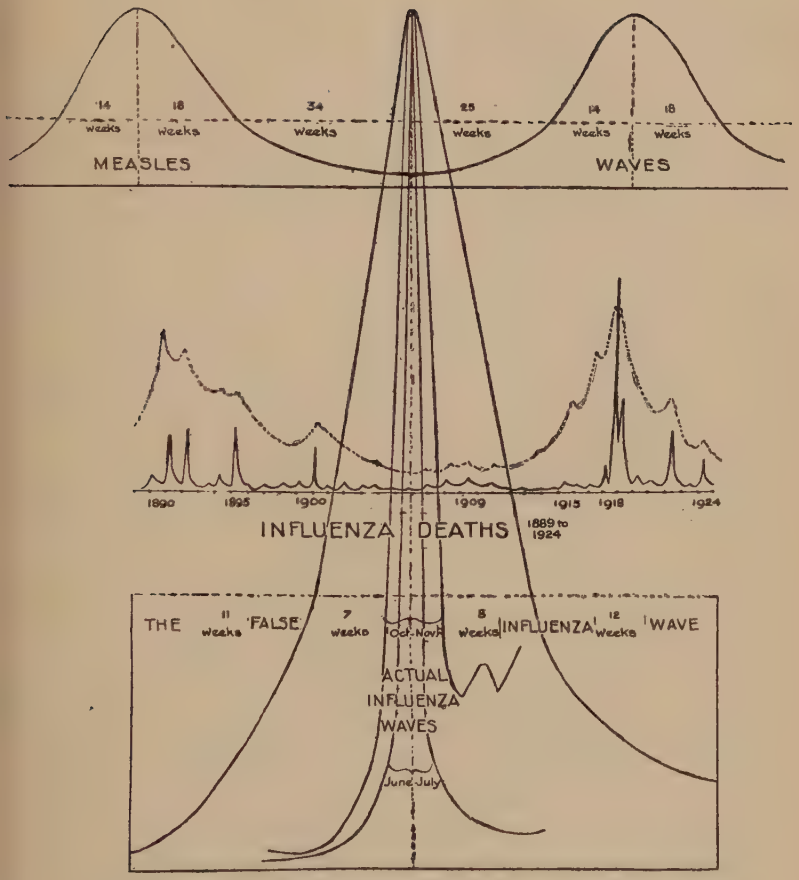
The impressions produced during these years were recorded in the Milroy Lectures, of 1906, on Variability and Persistency of type in Epidemic Diseases (25h). It was clear that, whether studied, in the several members of one family, or in associated prevalences of epidemic diseases in a community, influenza was remarkably variable and yet manifested a strange persistency even in its most bizarre manifestations. The writings of Creighton and Hecker on the English sweats inevitably prompted enquiry as to possible relationships with influenza. The history showed that influenza was pre-eminently, at any rate in the early centuries, a "Sweat." Moreover, the "Miliaires" and "Picardy Sweats" were also clearly blood relations. Yet another epidemic disease, which epidemiologically considered, claimed membership of the same family, was Dengue. Furthermore, enquiry regarding the form of the epidemic wave, in the simple case of measles, suggested comparison of the phenomena there revealed with those apparent in the far less stable influenza.

The three Milroy lectures thus sketched in outline a thesis correct, as now appears, as far as it went, but one needing much further amplification and development. The " trailers " following the influenza of 1890 had been predominantly pulmonary; those preceding the great pandemic of 1918 proved to be much more markedly cerebro-spinal in type. This striking manifestation of the " Protean tendencies " of influenza was particularly enlightening. For once, influenza was regarded by epidemiologists *not* as a " new disease," but acclaimed, for what it was—" The more it changed the more it was the same thing." As Sydenham (58a) said of the fever of his Fifth Constitution, "The fever was neither more nor less than what it had been throughout . . . its character being that of the family into which it is adopted " (M.O., V, v, 1-3); while the Constitution itself he describes (M.O., V, i, 7) as " exceedingly anomalous and irregular " and, he adds, " all the diseases which have originated from it have been the same."

This view was accordingly adumbrated, in a report of 1919 on the London Influenza of 1918-19, and it was set forth in far greater amplification in Dr. Crookshank's *Influenza : Essays by several authors* (10a), and in the Official Report of the Ministry of Health (38a). In the light of these findings, a further attempt to effect full and complete reconciliation between the new and the old epidemiology, between the twentieth century " Settings " of Whitehall and the seventeenth century " Constitutions " of Pall Mall, was made last year in a paper

on The Influenzal Constitution, in which Sydenham's doctrine of interaction between particles from the air, and the blood and humours of the human body, the former impressing a crasis upon the latter (M.O., I, 1-6), was placed side by side with Willis's parallel doctrine, outlined in his chapter on "Epidemical Fevers" (66a), and the two were studied in relationship with the modern conception of "an interaction between a virus and more or less immunised human communities."

Following upon the study made in 1906 of epidemic waves (25h), and beginning with the most simple example of such "interaction," it was pointed out (25n, 2) that "Measles in London, with its two-week incubation period has a wave-length of between eighteen months and two years; the corresponding elements in *pandemic* influenza, it was then maintained, might be taken roughly as one-third of a week (i.e. about one-sixth of that of measles), and, say, $\frac{\text{two to four years}}{\text{six}}$, or one-third to two thirds of a year." But influenza does not show anything like the stability manifested in measles, and allowance has thus to be made for variations exhibited, as one influenza-phase succeeds another, both in the germ and in the extent to which immunity is conferred upon its victims. In fact, study of influenza prevalences showed that the average wave-length above referred to (that at *pandemic* times), becomes extended, in trailers and precursors nearly adjacent to the pandemic prevalence itself, to eighteen months or two years, and even to as much as five to seven years in the trough between epidemics.



TYPES TO WHICH THE MEASLES AND INFLUENZA WAVES CONFORM.

Measles is shown above, Influenza below. The intermediately placed graphs show Influenza deaths, 1889-1924, and give a rough representation of the form of the Influenza wave during those years. For the explanation of the distinction made, in the lowest graphs, between "False" and "Actual" Influenza waves, reference must be made to p. 141 and to 25n, p. 60.

Upon this showing there certainly follows need of acceptance, for the purpose of filling in the picture, *first*, of the conception "influenza in mufti" or "endemic influenza," as postulated occupant of the trough between pandemic waves; and *second*, of that of an "influenzal constitution," undergoing gradual evolutionary development in the course of the centuries. The changes shadowed forth in this latter conception were, so far as it was possible to trace them in the records of the last five hundred years, displayed to view (*see* Frontispiece), and it was shown, working from the comparatively homogeneous to the more markedly heterogeneous, that a "moving continuity" of "influenzal constitution" could be discerned; beginning with the "composite portrait of the as yet not completely differentiated modern clinical types," seen in the "English sweats"; following these through the strange fevers (mainly pulmonary and cerebral), which made up the early "settings" of the influenzas; noting the gradual merging of these into the "pneumonia, typhus, relapsing fever," etc., of one hundred years ago; until, at length, the last-named prevalences became, in large measure, supplanted by certain epidemic diseases of the central nervous system.

Thus it was sought to demonstrate "the correlativity of these (symptom complex) opposites, and to show that they form inseparable elements of a higher (epidemiological) unity." Support for such a view was held (25n, p. 71) to be forthcoming in recent individual epidemiological experience; in the fact (*see* p. 138) that the London Bills of mortality yield evidence of the appearance

of influenzas " forming as it were the spray on the crest " of waves of fevers; and in the light of the statistical evidence (*see* p. 140) of the persistence of this phenomenon throughout " registration times " in London, provided always the changing fashions of disease nomenclature be taken into consideration.

Meantime, a considerable " Sydenham revival " was in progress. In 1919 Professor Greenwood (24a) read a paper on Sydenham. Dr. Crookshank's Chadwick Lectures had been delivered in 1918 (10b), and his *First Principles of Epidemiology* (10c) appeared in 1920. During the succeeding years he wrote the Essays published in 1922, and these aroused greatly increased interest in the study of epidemics from the natural history point of view, and tended to discourage meek acceptance by epidemiologists of a belief that all that was required of them was to rewrite epidemiology in terms of causal organisms. In 1927, moreover, Dr. Goodall read his paper on " The Epidemic Constitution " (21a); in which he began by commenting upon the revival of an old doctrine, references to which had disappeared from text books in the " eighties," and he gave as the principal reason for this decay, " the growth of the belief in the germ theory of infectious diseases."

Already before the war Peters discussed " epidemic potential " and the pioneer work of Ronald Ross and Brownlee was carried out (see p. 139); Topley and Greenwood, and Sheldon F. Dudley, in recent years, have further studied the theory of the epidemic wave.

There has, moreover, been very remarkable progress

in immunology. It was discovered that modern bacteriology had "outgrown Koch's postulates as Koch himself outgrew them." Moreover, bacteriology, it was agreed, had been hampered by carrying on routine work in aid of medical science, and to some extent had neglected its proper duty; Professor Boycott (2) a few years ago said bacteria had been "studied as causes of disease; no one has loved them for themselves."

It might, perhaps, looking at the question from a rather different angle, be maintained that at the close of the last century, Epidemiology and Bacteriology, like two modern babes in the wood, lost their natural parents and came under the care of a wicked uncle, essentially a practical business man, whose only concern seemed to be that they should completely lose touch, one with the other. Thus one was immured in a laboratory, while the other was brought up to perform routine duties in connection, first with collecting material for examination, and later with recommending segregation and disinfection in cases in which "positive results" were obtained; but now at length it has been made quite clear that the children should have been brought up together, learning one another's language, and becoming habituated to working in the closest co-operation.

The best results attainable are of course only to be looked for under such a co-education system, enabling the bacteriologist and epidemiologist of the future each to understand what the other is doing. Under the old conditions, misunderstanding was inevitable. Thus Sydenham's writings were declared to be mystic and his

" constitutions " were supposed to exclude all possibility of belief in germs. He was sometimes even said to have overlooked infection and to have ignored the protection afforded by one against another attack of infectious disease. A few months ago, when the sentences in the opening chapter of his Medical Observations were quoted as evidence that he clearly discerned the principles upon which modern immunology is founded, the suggestion was scouted as almost ridiculous; it was, nevertheless, on consideration, admitted that Sydenham never in terms, ruled out " ultravisible viruses." Presumably the critics really meant to draw attention to the facts that the Founder of Epidemiology was not wont to employ the terminology of Ehrlich, and was ignorant of modern work on agglutination and complement deviation. Carlyle says, " we have not *read* an author till we have seen his object whatever it may be as he saw it." Study of Sydenham strikingly exemplifies this saying. No one, moreover, having had first-hand experience of the influenzas round about the years 1918, and then encountering Sydenham's Fifth Constitution, could possibly doubt that he has seen the " stationary fever " Sydenham described very much as Sydenham himself saw it.

Dr. Crookshank has pointed out (10a, 10) that " Some difficulty has been introduced into discussion of the subject by the use, in two different senses, in Latham's translation of Sydenham's works, of the word *Constitution*. It has been used, and properly, to translate *Constitutio* (in the term *Constitutio Epidemica*) and then signifies a special order or arrangement, in a purely

phenomenological as well as in a conceptual sense. It is also employed in translating the expression (used by Sydenham) *pro occulta aëris diathesi* (M.O., I, ii, 2), as referring to " the inscrutable *constitutions* of the atmosphere "—a phrase better rendered by Swan, " according to the secret disposition of the atmosphere." As Dr. Crookshank says elsewhere (10d, 1) " The term *epidemic constitution*, as used by Sydenham, is merely the epidemiological equivalent of what for the military historian is a campaign, for the art student a ' period,' and for the viticulturist a vintage year. The doctrine itself—originated by Hippocrates, revived by Baillou, and expanded by Sydenham—merely implies that, during natural periods of time, the epidemiological happenings in any stated area tend to exhibit peculiarities and particularities that are more or less distinctive, just as during the reigns of particular kings, fashion, customs, art and literature tend to conform to the spirit of the times, and just as during a protracted war do natural periods of activity seem to be marked off as ' campaigns.' Further—and this is the particular contribution of Sydenham to the formal doctrine—it is believed that observation, if pursued by the historical method over long periods of time, will show that there is a tendency for the periodic recurrence of like epidemic constitutions." . . . Dr. Crookshank adds, " The empirical fact that epidemiological happenings are not disorderly, but a part of an organised process (when looked at from a wide angle), and the further fact that observation discerns natural periods in the epidemiological series, must be accepted, and do not necessarily imply

either disregard of what bacteriology has to say, or belief in ' atmospheric influences ' as causes of epidemics."

Chapter I in this volume, was prepared with a view to showing, *first*, that Sydenham's " Constitutions " and the " Settings " of the Ministry of Health Report of 1920 are just two different descriptions of almost identical groups of phenomena ; and, *second*, that Sydenham, at the close of his career, clearly apprehended the conception we now label " endemic influenza." The modern epidemiologist, therefore, should have no difficulty in visualising " the standard fever of Nature " of Sydenham, and in realising that there was nothing mystic about his " Epidemic Constitutions." One of the most interesting criticisms of the first draft of the scheme which Sydenham put forward, in the 1676 edition of his Medical Observations, is that of Freind (20), and this, as will be seen in the sequel, is the very criticism passed upon it by Sydenham himself in his later writings ; so that we may now all recognise that influenza, in densely populated areas, is an endemic disease—" the standard fever of Nature "—just as Sydenham declared it to be in the seventeenth century.

Chapter II gives a brief account of ten constitutions, eight described by Sydenham himself, and one preceding and one following this series. Three main conclusions may, it is then inferred, be drawn from Sydenham's writings. *First*, that his " intermittents " formed part of " the setting " of the pandemic influenzas and were not as a rule malarial fevers ; *second*, that his " stationary fevers " include, inter alia, all the fevers which go to make

up "endemic influenza"; and *third* (as Chapter II shows) that Sydenham gives in his writings descriptions of the *transmutations* of these fevers which may be classified under four headings—those occurring on the crest of a great pandemic wave, those nearly adjacent thereto on the downward slope of the wave, those of the trough, and those on the upward slope nearing the next great pandemic prevalence. Sydenham's contention, that the virus works more easily and rapidly near the crests of the waves (as we should phrase it) and with more difficulty and more slowly in the intervening troughs, is also considered in Chapter II, and compared with modern views concerning the influenza wave.

The two following chapters give account of "The History of Epidemiology during the last hundred years." The first discusses "Climates of Opinion," and shows that there have been four great epidemiological climates since the middle ages. Dr. Crookshank (10a, 3) has described them as (1) a period (like that of the English sweats), in which "wide epidemic prevalences were observed and compared without resolution into component diseases"; (2) a period of "Epidemic constitutions"; (3) an age of "describing specific diseases by the findings of morbid anatomy"; and (4) an age of "describing them by association with specific organisms". The commencement of the last hundred years covers some of the closing years of the third period and constitutes a very dark beginning, but one soon followed in the fourth period by progress in the matter of disease prevention, and progress, too, in the scientific study of

epidemiology. This fourth period showed, however, as Professor Whitehead noted (64b) a " tendency to stress specific distinctions and to overlook broad relationships "; and he, therefore, styled it the " Century of Professionalism."

The concluding Chapter shows how these difficulties encountered towards the close of the nineteenth century, were lessened, if they were not altogether explained away, by the teaching of Creighton as to the need for a " Return to Hippocrates "—to the natural history method of studying epidemic disease. The light thrown upon modern epidemics, by following up Sydenham's applications of this plan of procedure, is then illustrated in detail. A study is, moreover, made in this last chapter, of the special tendency of influenza to affect mortality in men of genius ; and finally the chapter ends by pointing the moral that in these modern days field observations and laboratory observations must be set side by side and studied together.

This preliminary survey would be incomplete, did it not make at least brief reference to questions, much canvassed during the last forty years, with regard to the bearing upon the theory of influenza of " terrestrial disturbances " and of climatic or " skiey influences." Creighton gave in his History full consideration to the former, discussing the generalities of Boyle, Arbuthnot, and Webster, but " declining to attempt to fit each historic wave of influenza with its particular earthquake, or to find the precise locality where clouds of infective matter had arisen, or the particular circumstances in

which they arose." He was "not the less," he said, (9c, 5) "persuaded of the direction in which the true theory of influenza lies."

With the modern study of the form of the epidemic wave—and acceptance of it as the outcome of interaction or interplay between a mutable virus and varying degrees of resistance offered by human hosts—the pendulum of opinion has tended to swing in the direction of the generalities of Arbuthnot rather than those of Webster; thus stress is now laid upon the human body as the *locus in quo* of development of the influenza germ, and not upon the bowels of the earth or upon the superincumbent atmosphere. Moreover, the emphasis placed aforetime, upon hiding places for contagion in remote sparsely inhabited countries now appears unnecessary, in view of acceptance of the thesis that influenza (sometimes, in a not easily recognisable form) is ever present, "endemic," in great centres of population.

Side by side with development of these conceptions, however, further progress has been made in quite recent times with regard to study of cosmic influences. Dr. Crookshank has given an account of this work in his "Some Problems: Influenza" (10d), and I am especially indebted to him for sight of a paper by Dr. Richter (50) of San Francisco, which deals in an exhaustive way with the question whether "Influenza pandemics depend on certain anticyclonic weather conditions for their development." This subject is one of great interest and, as Dr. Crookshank has pointed out, opens up such questions as that of "the ten yearly influenzal periodicity of

Stallybrass," of the " thirty-three year rhythm of pandemic influenza," and of their relation to " Brückner climatic cycles," of which the length is approximately thirty-five years, thus coinciding with Lockyer's thirty-five year cyclic variation in solar activities.

Dr. C. M. Richter starts with " the fact that pressure periods lasting a number of years (alternate) with similar periods of low pressure." Moreover, he says, " Changes in solar activity harmonise with and apparently cause such pressure periods " ; and " Influenza pandemics and pneumonia epidemics develop only during such pressure periods."

He adds, " Influenza pandemics of 1890, 1891, 1918, 1919 and 1920 prove this fact, as far as records are attainable, for the Northern Hemisphere and probably also for the Southern Hemisphere." Reference to his Fig. 1 enables comparison to be made, as regards twenty-two American cities, between annual air pressures (above and below the mean) and pneumonia mortalities, in certain of the towns.

There are some striking correspondences, but a number of failures are also apparent. In Fig. 2 more detailed information relating to 1918 is presented ; high pressure preceded the big October prevalence ; then early in October there was a fall of pressure in Boston, pressure increasing again about November 20th ; it is claimed that this second rise was followed by a second development of prevalence. Fig 3 gives details relating to 1919 and 1920 ; from these it appears that high pressure prevailed in the latter part of January, 1920, and this corresponds

with marked increase of prevalence in a number of cities. The phenomenon rather bears out similar observations in this country, which show that meteorological conditions operate even more conspicuously in " trailers " than in the pandemic prevalence.

Dr. Richter, as might perhaps have been anticipated, finds clearer indication of correlation between high pressure and pneumonia than between high pressure and influenza. He regards his pressure curves as quite reliable, but agrees (p. 9) that the figures giving pneumonia mortality are not free from error and, he says, " perhaps a reduction in the mortality line, since 1900, is to be attributed somewhat to the policy of the ' Census,' of eliminating many cases of pneumonia, that had been classified under ' primary cause of death.' " He agrees, moreover, that " Mean figures may be extremely misleading in certain years."

In his Table 4, on p. 21, which relates to " Influenza and pneumonia pandemics " and periods of high and low " Air pressure," out of nine groups of years in which the findings are compared, in only one, the first (1831-41), does there appear to be a striking positive correlation; as regards the second and third groups, the pandemic year 1847 comes just between low and high pressure periods, the fourth group occurs in a low pressure period without pandemics, the fifth, sixth and seventh are not specially remarkable, the eighth resembles the fourth, and the ninth (1902-1920) is classed as a " definite period of increasing high pressure," with the pandemics 1918-1920 occurring at its close. Dr. Richter notes further,

" The cities in Europe, generally, show the same years of minimum pressure 1878, 1885, 1893, 1901-2, and the same years of maximum, as in the United States, 1874-75, 1882, 1889-90, 1897-98, 1905-08." Elsewhere, he says (p. 7) " the years 1874-78 represented a low pressure period " in Europe. It should be noted that of the four groups of years, given above as years of minimum pressure, the two last named, 1893 and 1901-02, were years of considerable mortality from influenza in London ; while of the five groups given as years of maximum prevalence, only two, the first and third, were years of specially high mortality there.

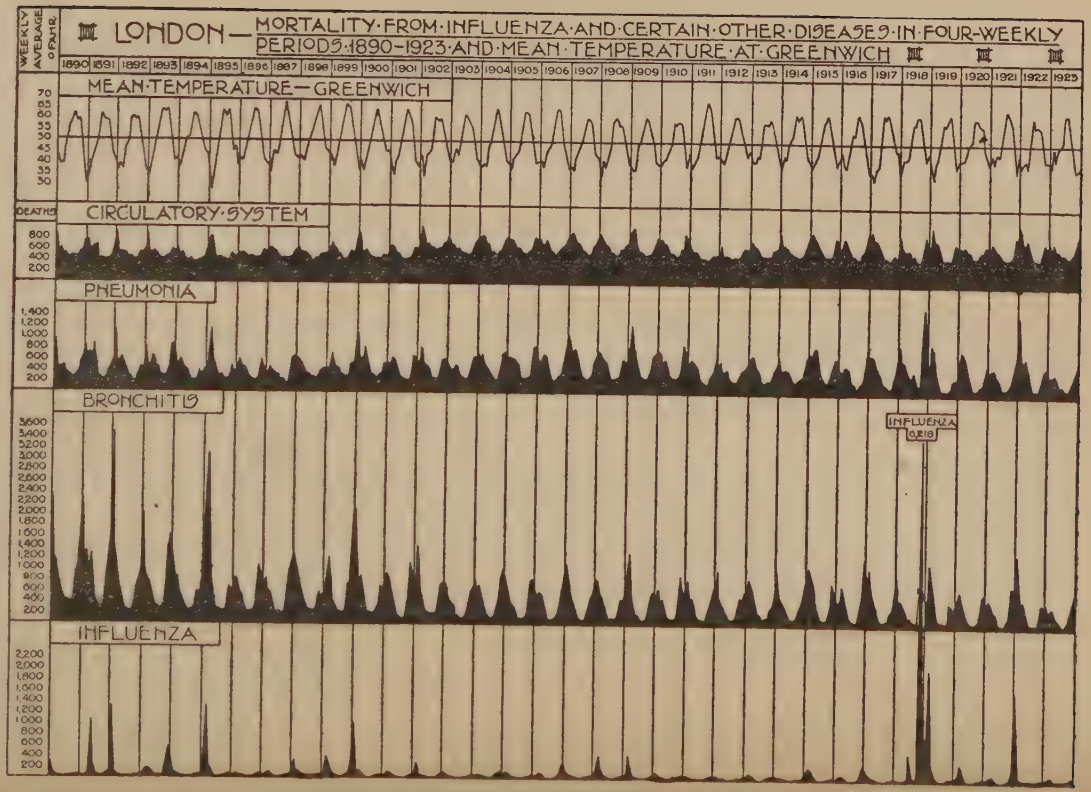
On p. 5, Nansen (40) is quoted to the effect that " In different groups of areas on the earth the meteorological elements (temperature, rainfall, barometric pressure, etc.) fluctuate or pulsate, so to speak, in time with one another, while in other groups of areas the fluctuations or pulsations are exactly inverted, and finally some areas show transition stages between the two." This observation confirms the truth of that of Dr. Richter, mentioned above, with regard to the misleading character of mean figures in certain years, and both ways of putting the case tend to suggest caution as regards relying upon concurrences between mean values (taken over a year or a series of years), in the case of air-pressures and mortality statistics. Moreover, when Dr. Richter speaks of " coincidence of gigantic departures of air pressure and gigantic epidemics " (p. 9) and cites as an instance of this (p. 21) the years 1902-1920, at the close of which the great pandemic of 1918-20 occurred, one naturally turns to his

Fig. 1, and finds that there, of his twenty-two cities, in only one instance Bismark, North Dakota, is the peculiar pressure development referred to conspicuously present. Dr. Richter apparently, however, attaches special significance to the Bismark station, for he says this station "Seems to act as the key to this long series of high pressure years, showing a rise of pressure from 1878 to 1919. It is the gate of the Alberta 'Highs,' which enter the United States in that region and then sweep over the United States in a southerly and south-easterly direction." There are no mortality figures given for Bismark but it stands alone in presenting such a long uninterrupted series of high years, and as its high pressure having passed the average in 1894 remained year by year continuously above this mean line, it would appear to have taken no fewer than twenty-four years for it to bring about the pandemic prevalence of 1918-20. It is important to bear in mind that this sequence of events is quite unparalleled by anything else in the records.

Franklin Parsons (45a) dealt with spread of the epidemic of 1889-90, not on the basis of yearly averages, but as exhibited in fluctuations occurring within months, weeks, or even days, and he gives (p. 101) reasons in support of his opinion that it was "propagated mainly, perhaps entirely, by human intercourse." His main points are that *progress* of the epidemic was independent of season or any particular kind of weather, that it did not travel faster than human beings could travel; that it did not occur among persons placed under circumstances precluding its communication by human agency;

that towns were affected before country places; that persons brought much in contact with others suffered early and that those in crowded places, institutions, etc., suffered together. It is evidence of this kind which must be considered in connection with Dr. Richter's first conclusion (p. 25) that "The assumption, that the propagation of influenza is analogous to that of an infectious disease, has so far no foundation in fact."

Dr. Richter's thesis "that the so-called cold weather diseases, or respiratory diseases, are not a function of temperature or humidity, but are dependent on certain high air-pressure conditions" would assume quite a different aspect if he were but content to regard descent of cold air from the "substratosphere" (five to nine kilometres above the earth), upon various regions of the earth's surface, in correspondence with individual anti-cyclonic distributions of pressure, merely as a *contributory factor*, which tends to accelerate the development of prevalence of influenza or to raise the death-rate caused by it. There can be no question that certain kinds of weather, often associated with east winds, are "neither fit for man nor beast," and these conditions, as already indicated, have again and again been associated with raised mortality from bronchitis and pneumonia and (in certain pandemic prevalences) with influenza. The Ministry of Health Report (1921) leans to the view that it is the low temperature, which is directly concerned in increasing mortality under these circumstances. The close correspondence in time, between low mean temperature at Greenwich, and London mortality from the diseases


LONDON — MORTALITY FROM INFLUENZA AND CERTAIN OTHER DISEASES IN FOUR-WEEKLY PERIODS 1890–1923 AND MEAN TEMPERATURE AT GREENWICH
WEEKLY AVERAGE OF QUARTER
1890 1891 1892 1893 1894 1895 1896 1897 1898 1899 1900 1901 1902 1903 1904 1905 1906 1907 1908 1909 1910 1911 1912 1913 1914 1915 1916 1917 1918 1919 1920 1921 1922 1923
MEAN TEMPERATURE — GREENWICH
70 65 60 55 50 45 40 35 30
DEATHS
CIRCULATORY SYSTEM
800 600 400 200
PNEUMONIA
1,400 1,200 1,000 800 600 400 200
BRONCHITIS
INFLUENZA 1918
3,600 3,400 3,200 3,000 2,800 2,600 2,400 2,200 2,000 1,800 1,600 1,400 1,200 1,000 800 600 400 200
INFLUENZA
2,200 2,000 1,800 1,600 1,400 1,200 1,000 800 600 400 200

depicted, is made apparent on the accompanying Diagram. The observations of Dr. Richter, however, with regard to high death-rates in camps in S. California and Texas in 1917-19, with a maximum of sunshine, tell against humidity and low temperature and favour air-pressure.

In considering how high air pressure conditions act, Dr. Richter refers to the possible influence of ozone, or something analogous thereto, some " product of unusual solar output." Sir James Jeans (31) recently spoke of the influence exerted upon the human body by " the radiation, which is the most fundamental physical phenomenon of the whole universe," and which is " so intense that it breaks up several million atoms in each of our bodies every second. It may be essential to life or it may be killing us." It is possible, of course, that this factor may play a part in favouring morbidity or mortality, or both, from certain " cold weather diseases." If this should prove to be the case it might account not only for excessive mortality from influenza and its associated cerebro-spinal, pulmonary and gastro-intestinal prevalences, but also for the well-recognised influence of like conditions upon measles, whooping-cough, tuberculosis and other diseases.

In contrast with Dr. Richter's " long period cycles " of cosmic influence, there stands the insistence of Brownlee upon a thirty-three week periodicity theory of influenza and in connection therewith upon the avoidance by influenza of the interval of time from the end of June to the beginning of December ; also the rival theory of

Mr. B. E. Spear that for each year "mortality maxima tend to balance about the commencement of the thirty-fifth week of the year." (See p. 67.)

In the London Annual Report for 1925 a note prepared by Mr. B. E. Spear (56a, 56b) is published in which reference is made to his criticisms upon Dr. Brownlee's periodogram analysis.

Mr. Spear writes: "The results obtained, on an assumption of Dr. Brownlee's thirty-three weeks periodicity and by the suggested method of balanced incidences are compared in the following table, in which are shown the errors in forecast of influenza prevalences in the years 1890-1924 inclusive, (I) on hypothesis of balanced incidence about the thirty-fifth week of the year, and (II) on hypothesis of periodicity of thirty-three weeks.

Method of Forecast.	Forecast too early by		Forecast correct to within 4 weeks.	Forecast too late by	
	14 weeks or more.	5-13 weeks.		5-13 weeks.	14 weeks or more.
I.	—	6	20	6	1
II.	2	6	8	9	8

"It may be of interest to note that the last prevalence of Influenza in London reached a maximum in the sixth week of the year 1925. This is twenty-nine weeks before the thirty-fifth week and, therefore, the next prevalence should occur twenty-nine weeks after, or about the eleventh week of the year 1926." This forecast proved to be correct within three weeks.

As Dr. Crookshank (10d) points out, moreover, "At the very foundation of the doctrine of the epidemic constitution lies an observed fact, implicitly or overtly recognised by Hippocrates, by Baillou and by Sydenham. It is this, that epidemic catarrhal prevalences, and prevalences of the nervous kind now familiar to us as encephalitis lethargica, as poliomyelitis, and the like, have always, though irregularly, tended to be chiefly manifested about the times of the equinoxes and, more particularly, somewhat *before* the vernal equinox—now the 21st March—and *after* the autumnal equinox—now the 23rd of September. Certainly there are eccentric variations, but the generalisation holds true, and there is a seasonal incidence of the kind indicated, in all years."

It will be observed from this general survey of time-relationships that the results do not appear to conflict with the view that the long interpandemic wave of thirty-three years or thereabouts, the ten or eleven year smaller wave described by Stallybrass, and in less degree the minor approximately biennial, annual and still smaller wavelets, are all primarily associated with interplay between a virus and its more or less immunised hosts. In other words, there does not seem to be a case for concluding that the major and minor waves of influenza are exclusively conditioned by cosmic influences; it would seem rather that influences of high pressure, low temperature, etc., are superadded upon those biological conditions which primarily determine the form of the great pandemic waves; the superadded factors thus

playing the smaller though by no means insignificant rôle of helping to fix the approximate times of maxima, both of the pandemic waves, and of the minor wavelets seen on the slopes of the great ocean rollers of influenza.

It is of peculiar interest to find that some such method of approaching the problem of climatic influences commended itself to Sydenham, who says (IV, iv, 3):— "It must be observed that although the manifest qualities of the atmosphere may not impress the same influence upon all constitutions alike, so as to originate all those epidemics which are referred to it, as to their productive cause, they can nevertheless influence them for a time, so that epidemics are admitted or excluded, as the manifest qualities of the air oppose or favour them."

Finally, it must not be forgotten that animals are apt to suffer from epidemic disease, at about the times when influenza affects man. The analogy between influenza of horses and influenza of man was discussed by Lt.-Col. A. J. Williams (65) in a recent paper; and epidemic Encephalitis in Dogs has been described by Leslie P. Pugh (48) as closely resembling Encephalitis lethargica in man, "both in symptomatology and in the character of the cerebral lesions."

In the absence of conclusive laboratory evidence of the existence of an ultravisible virus there is a tendency to impose upon epidemiology the duty of explaining the "settings" of the great pandemics, amid pulmonary, cerebro-spinal and gastro-intestinal prevalences, and of

probing more deeply into the secret of "endemic influenza." Upon both these questions a flood of light was thrown by Sydenham, and the main purpose of the present undertaking is to set out, as concisely as may be, the considered outcome of his enquiries, as expressed in the *Medical Observations* and in his later writings.

Postscript. Since the present work was completed two books incidentally throwing further light upon its main argument have appeared. *The Genesis of Epidemics*, by Lt.-Col. C. A. Gill, most fascinatingly elucidates the "Unitary Mechanism of Epidemics" and discusses "Epidemic Constitutions," with—at any rate so far as Influenza is concerned—a disposition to favour the Sydenham point of view. The second book referred to, the *Report of the Committee on Vaccination*, of July, 1928, examines the evidence in connection with recent reports on encephalitis following after vaccination, here and in Holland. The Committee endorses the conclusions of the Andrewes Committee, of 1925, regarding these occurrences. Both Committees (the former, with a single dissentient) dismiss the hypothesis of "cerebral vaccinia" and (perhaps with less confidence) that of "fortuitous overlapping," while both incline to accept an "hypothesis of combined vira."

The discussion of the question, whether or no there was a mere "fortuitous overlapping" between vaccination and encephalitis, is commenced on p. 102, reverted to on p. 119, and finally commented upon by the second Committee on p. 170; but even then the reader may feel that it is not definitely settled. Dr. Greenwood (p. 102) was appealed to and found that "the fatal incidence of nervous disease was somewhat higher on recently vaccinated and revaccinated children than on the general population of like age." An attempt was then made by the first Committee to undertake intensive study of "post-vaccinal cases" in Gloucester and Worcester, the two counties supplying thirteen such *cases* during the summer months of 1923. This analysis adds, however, no real weight to Dr. Greenwood's examination of *deaths*, inasmuch as only two of the thirteen cases (v. Table on pp. 129-144) were definitely ascribed to Encephalitis lethargica and are thus the only cases that can be said to be quite fairly comparable with the 19 + 36 cases of notifiable disease referred to (on p. 170) as occurring during 1923 among the unvaccinated children of like age in the two counties. Moreover, it is carefully pointed out by the first Committee (p. 120) that the "constancy of the so-called incubation period may be more apparent than real."

The outstanding interest, however, speaking epidemiologically, is the near approach on the part of both Committees to the view of Sydenham, that there are gradations, modifications and affinities among epidemics occurring in successive cycles of years and that in certain connections such epidemics must be considered as a whole. Moreover, both Committees are disposed, as Sydenham was, to assume that one virus may conceivably influence another.

CHAPTER I

1915-1925

The Recent Influenzas

The raison d'être of this chapter is not, of course, the advocating of a crusade for promoting the substitution of "new lamps for old." On the contrary, the writer believes that the guidance of the search-lights, of all the centuries of epidemiological history, is needed for the successful navigation of a very difficult stretch of coast; the light, moreover, to which he desires to direct special attention is that of Sydenham which shines far away back in the middle of the seventeenth century; for it will be apparent, in the sequel, that it sheds illumination of vital importance for present-day voyagers. While claiming, however, the right to range at large over the whole domain of Geographical and Historical Pathology, and feeling restive when held within the four walls of the here and now, the writer admits that we can only attempt to interpret the past in terms of the experience gained in our own little patch of immediacy, and so we naturally turn first of all to the happenings of 1915-1925, which may still almost be said to belong to what philosophers term the "specious present"—while reference may perhaps be now and again permitted to memories

of " the nineties," which are also, of course, fresh in the minds of many of us. The history of the prevalences of 1915-1925 may best be considered under three heads—the Precursors of the Great Influenzas of 1918-19; those Influenzas themselves; and the Trailers following after them. The first and the third series will, however, be more particularly discussed, for detailed reference to the Influenzas of 1918-19 would seem almost superfluous; moreover, it is their " setting," rather than the pandemic prevalences themselves, that here mainly interests us.

It may be observed at the outset, that the stage was, as it were, carefully prepared for the happenings of the years 1915-25 just at the very moment when the drama was about to commence. From the *epidemiological side* there had been for many years a growing recognition of the folly of hailing, as " new diseases," wide-spread epidemic prevalences concurrently developed in various parts of the world; of laying stress in one country upon their sweating character, in other countries upon their proclivity for attacking the brain and spinal cord, or lungs, or gastro-intestinal tract, more exceptionally (and notably in tropical countries) upon manifestation of skin eruptions, and so forth; for the very simultaneity of these aberrant occurrences suggested the probability that the variously described " new diseases " stood in close relationship one with another.

Again, on the *bacteriological side* it was clear, early in the present century, that there had been too much insistence upon " seed " as against " soil." The great battles of the " eighties " and " nineties " between the

Kochs and the Pettenkofers—the "contagionists" and "localists"—had resulted in the triumph of the former, but it was soon apparent that it was somewhat of a Pyrrhic victory. The administrative difficulties associated with "stamping-out methods" on contagionist lines, in diphtheria and typhoid fever, became obvious as soon as the actual numbers of "healthy carriers" were realised. Moreover, Sir Douglas Powell had pointed out, in another connection, that "control of tuberculosis involves something more than the circumvention of a bacillus"; and the work of Karl Pearson and others emphasised the paramount importance of soil and of environment generally; while (25, f. i) it became further recognised that much misunderstanding with regard to tuberculosis mortality had been occasioned by failure to take due account of the influence of migration, from one part of the world to another, of actual or potential sufferers from the disease. Again, as already noted, discovery of the fact that the hog-cholera bacillus was merely a secondary invader greatly stimulated study of ultravisible viruses, and thus indirectly tended to bring about closer understanding between the practical administrator and the working bacteriologist.

Much light upon the problem now seen to assume importance was thrown by study of difficulties arising in connection with influenza. It had been recognised that the trailing prevalences of the "nineties" were influenzas (Pfeiffer's bacillus or no Pfeiffer's bacillus) and later outbreaks drove this truth home. Brorström (3) worked out the connection between influenza and

poliomyelitis in the prevalences of 1905-07 in Sweden; nearer at hand, in East Herts, the " outbreak simulating influenza," (13) with its cerebral, pulmonary and gastro-intestinal types and its skin eruptions, was described by Dunn and Gordon. Then the Glasgow and Belfast outbreaks of cerebro-spinal fever followed in 1907, and the relationship of these occurrences to influenza elsewhere was suspected, and, in London, cerebro-spinal fever having been made notifiable, the sporadic cases were carefully studied by Wanklyn (62). These occurrences heralded the approach of the storm.

THE PRECURSORS OF THE GREAT INFLUENZAS OF 1918-19.

At length, in 1915, cerebro-spinal fever assumed epidemic proportions in London. and soon afterwards the great outbreak of poliomyelitis developed in New York. The association between influenza and cerebro-spinal fever in London was, from the outset, made the subject of study similar to that already initiated by Brorström in Sweden. A questionnaire was drawn up and Borough Medical Officers of Health undertook to make careful enquiries into all notified cases. The results of this work were subjected to statistical examination by Mr. G. H. Day, whose conclusions are set out here, in considerable detail, for they are of fundamental importance, illustrating as they do the difficulties of such an enquiry, and at the same time establishing the fact that the closeness of the relationship between influenza and cerebro-spinal fever is beyond all question. The following extract

from the London Annual Report for 1914 gives the outcome of this research.

"It appears that, of sixty-one patients notified, during the year 1914, concerning whom particulars were obtained, twelve gave a history of having recently suffered from colds; and contact with cases of influenza, cold or sore throat was noted in four cases. During the period 1st January to 22nd May of the year 1915, however, when influenza was prevalent, 523 cases of cerebro-spinal fever were reported and among the 462 cases concerning which particulars were obtained there was a history of recent influenza in thirty-seven instances, and in twenty-seven of these the patient was said to be suffering from influenza within seven days of the onset of symptoms of cerebro-spinal fever. Colds, sore throat, cough and catarrh were noted as having affected seventy patients prior to attack of cerebro-spinal fever and ten patients had recently suffered from pneumonia. Contact with cases of influenza, colds, etc., was noted in sixty-six instances.

"The number of cases giving a history of recent attack by, or contact with, cases of influenza is certainly large enough to afford justification for further examination. The main point to be determined is whether the number of cases of cerebro-spinal fever giving such a history (of (*a*) recent attack by, and (*b*) contact with cases of influenza) is *greater than might have been expected as a matter of chance*. The determination of the probability of the occurrence of (*b*) would necessitate the use of some hypothetical figure difficult of ascertainment

and it was therefore decided to limit consideration to (*a*).

"It was felt that some indication of the prevalence of the disease in the general population of London might be afforded by an examination of the staff returns of illness furnished by the various departments of the London County Council to the Establishment Committee. These returns relate to some 3,000 officials . . . (the population is not a random sample of the London population as a whole, but reasons are adduced for holding that any error thereby introduced would not be appreciable). . . . The figures shown in column 3 of the following Table have, therefore, been calculated on the assumption that the cases of influenza occurring in the London population were proportionate to those occurring among the Council's staff.

"In explanation of the Table, it may be stated that column 2 shows the number of cases of influenza occurring among 3,000 of the Council's staff in each week; column 3 shows the result of applying the figures in column 2 to the London population, and gives the estimated number of cases of influenza in each week, which might be expected to have occurred in the London population; column 4 shows the proportion of the London population attacked in each week, based on the figures shown in column 3; the fractions representing this proportion express the probability that a case of cerebro-spinal fever selected at random in the corresponding week will give a history of recent attack by influenza; column 5 shows the number of cases of cerebro-spinal fever occurring in

Week ending.	Cases of reported influenza among 3,000 of Council's staff.	Estimated cases of influenza in London population based on L.C.C. staff returns.	Proportion of London population attacked by influenza in each week.	No. of cases of cerebro-spinal fever occurring in each week.	No. of cases of cerebro-spinal fever giving a history of suffering from influenza within seven days of onset of cerebro-spinal fever.	Probability (p) of the occurrence of the number of cases shown in previous column.
1915						
Jan. 9	16	24.000	$\frac{1}{187}$	6	—	.9683
„ 16	14	21.000	$\frac{1}{214}$	6	—	.9723
„ 23	27	40.500	$\frac{1}{111}$	6	—	.9472
„ 30	21	31.500	$\frac{1}{143}$	11	—	.9257
Feb. 6	24	36.000	$\frac{1}{125}$	8	2	.0017
„ 13	19	28.500	$\frac{1}{158}$	14	4	.0000
„ 20	19	28.500	$\frac{1}{158}$	25	2	.0104
„ 27	26	39.000	$\frac{1}{115}$	19	2	.0111
Mar. 6	15	22.500	$\frac{1}{200}$	40	2	.0161
„ 13	17	25.500	$\frac{1}{176}$	29	4	.0000
„ 20	21	31.500	$\frac{1}{143}$	34	—	.7877
„ 27	20	30.500	$\frac{1}{148}$	37	1	.1958
April 3	14	21.000	$\frac{1}{214}$	14	2	.0019
„ 10	14	21.000	$\frac{1}{214}$	56	4	.0001
„ 17	12	18.000	$\frac{1}{250}$	43	—	.8417
„ 24	8	12.000	$\frac{1}{375}$	27	1	.0672
May 1	9	13.500	$\frac{1}{333}$	19	1	.0541
„ 8	6	9.000	$\frac{1}{500}$	26	1	.0495
„ 15	3	4.500	$\frac{1}{1000}$	22	—	.9782
„ 22	2	3.000	$\frac{1}{1500}$	20	1	.0132

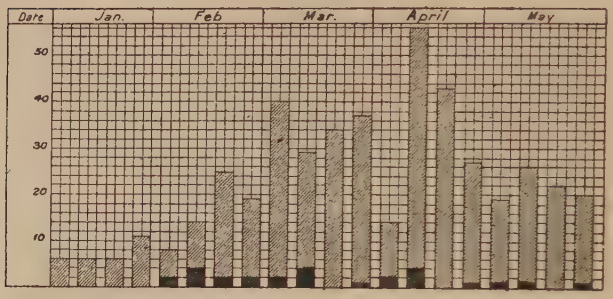
each week and column 6 the number of these cases giving a history of suffering from influenza within seven days; column 7 shows the probability of each of the occurrences shown in column 6. The facts shown in columns 5, 6 and 7 of the Table are exhibited graphically in sections I and II of the diagram on page 40.

"It will be seen from the Table that in thirteen out of the twenty weeks investigated cases of cerebro-spinal fever occurred, giving a history of suffering from influenza within a week of attack by cerebro-spinal fever. The probabilities of such occurrences are shown in column 7 and the values of (p), the probability of the occurrence of the number of cases shown in column 6, are so small as to raise question whether the occurrence of influenza and cerebro-spinal fever in the same person within the limited period can be regarded as independent events.

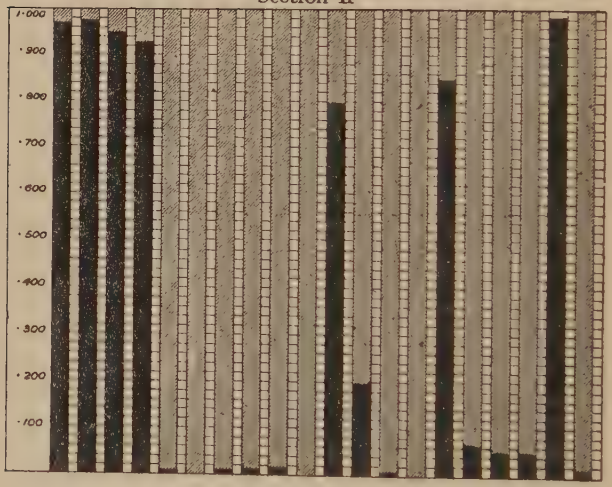
"If the figures for the whole period under review be taken, it will be seen that of 462 cases of cerebro-spinal fever twenty-seven gave a history of suffering from influenza within seven days of the onset of this illness. The probability of the occurrence of so large a number of cases, assuming attack by influenza and cerebro-spinal fever within the limited period to be independent events, works out at a figure which is practically infinitesimal. It will be seen from section III of the diagram that the most probable number of cases giving a history of recent attack by influenza is two, and that the successive probabilities of obtaining 3, 4, 5, etc., cases rapidly decline, the probability of obtaining seven cases, for instance, falls as low as .0077; beyond this point it is unnecessary to

DIAGRAM ILLUSTRATING CERTAIN ASPECTS OF THE RELATIONSHIP BETWEEN CEREBRO-SPINAL FEVER AND INFLUENZA.

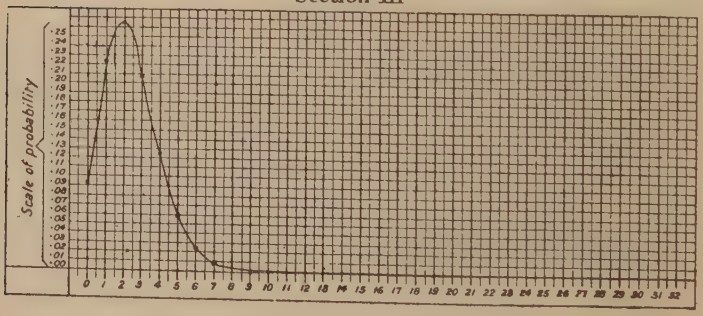
Section I



Section II



Section III



Section I. In this section of the diagram the height of the columns represents the number of cases of C.S.F. notified in each week of the first five months of 1915. The height of the deep black portion of the columns represents the number of cases of C.S.F. giving a history of attack by influenza within a week of the onset of attack by C.S.F.

Section II. In this section of the diagram, if the total height of the columns be taken to represent "certainty," then the height of the deep black portion of the columns represents the probability of the respective "happenings" indicated in Section I of the diagram.

Section III. This section of the diagram is calculated over the whole period of the outbreak and shows the probability of the occurrence of 0, 1, 2, 3, etc., cases of C.S.F., giving a history of attack by influenza within a week of the onset of attack by C.S.F.

calculate the ordinates of the probability curve, but the sum of the probabilities of the first eight ordinates gives a figure of .9964; the probability of obtaining eight or more cases with an influenza history is, therefore, the difference between .9964 and unity, viz., .0036. It will thus be seen that the probability of obtaining more than seven such cases is less than four in 1,000, whereas the number of such cases actually recorded reaches the high figure of twenty-seven.

"The facts set out in the preceding paragraph may perhaps be more clearly appreciated if presented as follows: suppose that 462 persons are chosen at random from the London population, in groups of from twenty to thirty during each week of the first five months of the year 1915; one would expect, having regard to the prevalence of influenza during these months, to find that some two or three of the 462 people thus chosen would be either suffering from or recently recovered from an attack of influenza; turning, however, to the "selected" group of 462 sufferers from cerebro-spinal fever we find that not two or three, but as many as twenty-seven give a recent history of influenza attack. This latter number (twenty-seven) compared with the 'expected' is so large as to afford strong ground for the belief that some relationship exists between the two diseases. This presumption is materially strengthened when regard is paid to the large number of cases of cerebro-spinal fever giving a history of contact with sufferers from influenza."

The Annual Report of the M.O.H., County of London,

for 1915 (25i, 1), discusses the "extent to which the development of cerebro-spinal fever occurs, in the civil population, among those who have been associated with soldiers or whose homes have been visited by soldiers." This enquiry afforded "an interesting control experiment for testing the significance of the relationship of cerebro-spinal fever and influenza." The percentage of returns relating to cerebro-spinal fever in civilians, in whom association with soldiers was recorded, was found to be much lower than the percentage of those giving a history of influenza or catarrh, or of contact with sufferers from influenza or catarrh.

The Annual Report for 1916 (25 i, 2) gives a Table showing the relationship between cases of cerebro-spinal fever and influenza, coughs, colds, catarrh, etc., in six successive epidemic and non-epidemic periods, between January, 1914, and April, 1917. The percentages of cases giving a history of suffering from, or one of being exposed to infection by, an illness resembling influenza, just precedent to attack by cerebro-spinal fever, to the total number of cases in the six periods, were as follows :

Three Epidemic Periods.	*Three non-Epidemic Periods.*
Jan.-May, 1915, 12.0 per cent.	The year 1914, 1.6 per cent.
Jan.-April, 1916, 5.1 per cent.	June-Dec., 1915, 1.4 per cent.
Jan.-April, 1917, 9.1 per cent.	May-Dec., 1916, 2.4 per cent.

The fact that notably higher percentages were found in the epidemic than in the non-epidemic periods is deserving of note.

In the meantime, a discussion on cerebro-spinal fever had been held at the Royal Society of Medicine, and in the

Transactions for 1915 (25k) a parallel was drawn between the happenings in the London of to-day, and those of 250 years ago. The following extract from the Transactions may be quoted. "The early account was that of an old London practitioner, who prefaced his remarks by saying that he was 'At an advanced age and of a weakened constitution, which fairly gave him a title to spare himself the pain and labour of any intense thought and meditation'; nevertheless, he thought it worth while to put on record what he had observed about this particular outbreak. He said it 'commenced in February, and the patient often had chills and flushes by turns, and frequently complained of pains in his head and joints and generally had a cough. There was also pain in the neck and fauces; the fever was continued, and the patient might determine the fever to the brain and convert it into a frenzy. Petechiæ were apt to show themselves, and in young and sanguine subjects there might be purple blotches; if the patient were heated the perspiration would be clammy. If matters were mismanaged, the spirits were wholly thrown into confusion, an inordinate pulse set in, there was a jerking of the limbs, and death took place. Of all the fevers (this practitioner had ever seen) this attacked the brain most, and could not be detached from it without great trouble and danger. "These sentences were taken from Sydenham's description of what he called the 'new fever' of 1685. There was nothing there recorded with reference to Kernig's or Babinski's signs, nor was there any mention of the meningococcus, or of the parameningococcus; yet there

could be little doubt that Sydenham must have been describing the disease, which they had been studying (in London, at any rate) during the past eight or ten weeks. During those weeks they had had the evidence presented by the deaths announced in *The Times*, and they had noted the excessive numbers of people who had been recorded by the Registrar-General as dying from bronchitis and pneumonia, and as dying from influenza. There had, too, actually been a small increase in the number of deaths registered from cerebro-spinal meningitis. There were the strongest reasons for believing that Sydenham's description could be very well accepted as giving a fair account of the epidemic now prevailing.

"The fact was, that the bacteriologists could not see the wood because of the trees. If Sydenham were back here among us and he were told that the influenza-like cases in the present epidemic were due to Pfeiffer's bacillus, and the sore throats were due to the Micrococcus catarrhalis, and certain other conditions were due to pneumococci or to streptococci, and others to meningococci, and yet others to parameningococci, he would laugh when he realised that such crude notions were seriously entertained. He would probably tell us that the germs which the bacteriologists were demonstrating were nothing more than 'associated organisms,' or 'secondary invaders.' If we could only bring ourselves to look at the matter from that point of view we should be able to entertain broader and more philosophical notions with regard to ætiology, more rational ideas as regards prevention, and he thought, too, that there would

be more hope in respect of treatment than could be entertained as long as men's minds were obsessed by the existing theories."

Question was raised in the same discussion as to whether these concurrently developed prevalences were merely associated with one another, as the outcome of certain common environmental influences (climatic and other), or whether the concurrences really implied some biological relationship between the epidemics. This point was later more fully considered in the discussion on Influenza (25m 1), the following reasons being adduced in support of the latter view.

"An important argument in favour of a *common infecting agency*, in the first named influenzal group of diseases, is forthcoming on applying the principle known as the Law of Parsimony. In an influenza outbreak the cases of 'influenza' are numerous, the cases of bronchitis and pneumonia less common, those of cerebro-spinal fever, poliomyelitis and encephalitis lethargica, comparatively speaking, rare. Let us take one of these for purpose of computation, say, cerebro-spinal fever. Sir Arthur Newsholme in an introductory memorandum, of last year, to *Further Reports on Cerebro-spinal Fever*, dealt with the relation of case-rate to carrier-rate. He calculated for London during 1916, on a two per cent. 'non-contact carrier-rate' basis, each carrier only circulating among ten persons during the course of a year (a basis which is admittedly too low), that the number of the carriers of the meningococcus was about 800,000; hence on a ten per cent. basis, which Sir Arthur accepts (though,

he says, it is if anything, an underestimate), the entire population of London would, at one time or another during 1916, be acting as carriers of this organism. If this be agreed, it might then be inferred that similarly during the year the whole population (or something very little short of it) acted as carriers of the corresponding organisms concerned in spreading bronchitis, epidemic catarrh, pneumonia, influenza, poliomyelitis, and encephalitis lethargica, so that nearly everyone harboured the several contagia of all these epidemic diseases during the year. In cannot fail to be appreciated, however, that the alternative hypothesis, that there is *one common infecting agency*, at once fits the facts and greatly simplifies the necessary assumptions. I venture, therefore, to plead for the application of William of Ockham's razor : 'Entia non sunt multiplicanda praeter necessitatem' to the present case. The use of this instrument would not only reduce by some millions, in London alone, the number of the carriers of the causal agent, many or all of whom are regarded, by whole-hearted suppporters of the healthy carrier doctrine, as persons who should be segregated ; but it would also enable a consistent workable theory of the case-to-case spread of influenza, now in pandemic waves and now in intercurrent trailing epidemics, to be formulated. It would by focussing attention upon one single cause instead of upon a congeries of secondary invaders, give research workers and statisticians a chance of studying the laws of influenzal epidemicity, and—a consummation devoutly to be wished—at the same time relieve that much harassed

Sindbad, Preventive Medicine, of the need of carrying on his shoulders an old man of the sea in the shape of an impracticable working hypothesis."

Following hard upon the cerebro-spinal fever of 1915 came the great poliomyelitis of the next year, which was fully described in New York in a detailed report; moreover, a careful discussion of the American epidemics of this and the immediately following years will be found in Dr. Dwight M. Lewis's paper (35, 1). The conclusion is there formulated that " The various waves of the so-called pandemic of influenza were caused by consecutive and increasing prevalences of correlated diseases due to the activation of carriers of the organisms of these diseases, whether by the influenza bacillus or by the streptococcus." Moreover, Dr. Lewis says, " The chief source of confusion and difficulty in our endeavours to understand the ætiology and prevention of influenza epidemics has been the persistent way in which, from the bacteriological and epidemiological points of view, certain *correlated* organisms have been considered as the organisms of independent, autonomous and unrelated diseases " (35, 2). Work of a character closely resembling the above was at about the same time being undertaken, at Chatham, by Col. J. Dorgan (12).

On Nov. 24th, 1916, the then recent London prevalence was described in a paper (25h), in which reference was made to Ozanam's descriptions of encephalitis developing concurrently with epidemic catarrh or influenza, to the remarkable time relationships between Hirsch's prevalences of cerebro-spinal fever and influenza,

and to the two possible hypotheses with regard to phenomena such as these, with more particular reference to recent happenings in London. Thus, it was pointed out that " On the one hand the disease (cerebro-spinal fever) may be regarded as a complication or sequela of influenza, it being assumed that owing to special circumstances some individuals, when attacked by influenza, develop cerebro-spinal fever, and thus to the infection of influenza is superadded the complication of involvement of the central nervous system. On the other hypothesis, cerebro-spinal fever and influenza are held to be quite distinct diseases ; if cerebro-spinal fever appears at all it is developed quite characteristically, and in order to explain sporadic occurrence of the cases, it is assumed that apparently healthy persons may transmit the causal organisms. The arguments for and against these two rival hypothesis were set out in extenso.

THE GREAT INFLUENZAS OCCURRING ON THE CREST OF THE PANDEMIC WAVE OF 1918-1919.

The London Annual Report for 1917 (written in May 1918 (25i, 3) sets out the " three striking characteristics" held to be "epidemiologically-speaking diagnostic of the then prevailing type of epidemic influence —(i) its ' posting character,' (ii) its ' power of impressing the mind of observers as being a new disease,' and (iii) its ' protean manifestations.' " This report also discusses the change of phase of the " epidemic influence," announced in this country, April 7th, 1918, by two papers

in the *Lancet* suggesting that the "new disease" was "botulism." This phase was later officially described by the Ministry of Health as the "Obscure disease with cerebral symptoms," and it still later became generally known as "Encephalitis lethargica." Dr. Crookshank's Chadwick Lectures (10b), which set out the history of Encephalo-myelitis throughout the whole period of available records, made it abundantly clear that encephalitis lethargica, at any rate, was not a "new disease."

The prevalences of 1918-19 have been fully considered elsewhere in various official reports, and have been made the subject of very careful comment in the volume already referred to, edited by Dr. Crookshank (10a). As regards London, the outbreaks of 1918 and the early part of 1919 were described in a special report to the London County Council published in June, 1919 (25j). The "first beginnings" are referred to on pp. 1-3 of this report, the anomalous age-incidence observed in the influenzas of the two years is discussed on pp. 6-7, and a summary view of the development of an "influenzal constitution" during a series of years is given on pp. 15-17. It is there pointed out that, "As Creighton has observed, influenza can be 'identified as certainly in the brief phrases of mediæval chronicles as in elaborate modern descriptions'; by his careful analysis of the facts he has, moreover, securely established the close relationship between epidemics of influenza and epidemics of ague; it is now, moreover, claimed that these remarkable related agues consisted of the fevers with gastro-intestinal, pulmonary or nervous complications, which

are becoming recognised as constituting the disease types the Proteus influenza is apt to assume. Attention has been more especially devoted in the present enquiry to cerebro-spinal fever (in London), because it has been possible to pick out (past) epidemics of this disease, like blackberries from a bush, in Creighton's great historical chapter on typhus and the continued fevers. A similar harvest has, however, been collected by Dr. Crookshank (10b) from the literature of the Heine-Medin disease, and had materials relating to epidemic pneumonias or epidemic bronchitis been in like manner available, this field of enquiry could also doubtless have been exploited with profit."

Two further points are then mentioned. "*First*: It should be realised that influenza pandemics did not in the nineteenth century affect all parts of the civilised world simultaneously, there was, indeed, a tendency to alternate between the Eastern and Western hemispheres, Europe suffering more in 1780-82, America more in 1798-99, Europe about 1800, America almost exclusively in 1815-16, and again in 1826-27, Europe much more about 1831, America in the summer of 1843, Europe later in the "forties," America in the early "fifties," while both were involved to a practically equal extent in the "seventies" and "nineties," and in 1916-18 (see Frontispiece). *Second*: It is important to note that the constitutions extend over more years in the later centuries than in the earlier, and arising out of this it will be clearly discerned that the state of the population concerned, as regards freedom of communication

with the world at large and also as regards immunisation by previous attack, has momentous influence in determining duration of the constitution and the behaviour generally of the epidemic disease."

The concluding paragraphs of the Report (25j) deal with "some of the factors governing the form of the influenza wave," and as the outcome of this, the following exposition of the contrast between an original (pandemic) prevalence and the next succeeding prevalence was made, and a forecast of the probable later epidemic happenings was given as follows:—In the former, "Persons who mix freely with their fellows are specially likely to be attacked; in the latter young children and old persons will suffer in larger proportion. In the former, the prevalence will be widespread, the mortality comparatively low; in the latter, the pulmonary complications among old persons and children, and the nervous complications in children, will render the case-mortality much higher. The first trailer will not spread so quickly as does the pandemic prevalence, partly because its predecessor skimmed off the cream, as it were, of the susceptible material (i.e., of those who mix with the world and are thus specially likely to be attacked), and partly because some of those attacked may have acquired partial immunity in the previous attack.

"As 'trailer' succeeds 'trailer' the cerebro-spinal and pulmonary complications assume greater prominence, the prevalences are more prolonged and tend to recur at longer intervals, and the striking power of individual cases becomes less marked. After the lapse of six to eight years

the characteristics exhibited by influenza in its pandemic phase become greatly obscured, and, save for slight annual increase in the mortality from pneumonia, bronchitis, etc., the very existence of influenza in a town like London may be almost entirely lost sight of. Gradually, however, protection of the population again wanes, and after a while anomalous illnesses, cerebro-spinal fever, polio-myelitis, epidemic pneumonia, again begin to attract attention; then later perhaps lethargy and other protean manifestations of influenza present themselves, and, at length, the moment arrives when the town suddenly realises that it is in the grip of something which it feels can only adequately be described as a 'new disease.' "

Some very arresting and important observations upon the "setting" of an influenza epidemic appear in the special *Report on the Pandemic of Influenza* (1918-19), published by the Ministry of Health in 1920 (38a). The *relation of influenza to other contemporary diseases*, and the question whether there is an "epidemic constitution" of influenza, are discussed as follows :—

"To answer these questions we must consider our growing experience of the 'setting' of an influenza epidemic. Attention is drawn in the report to various epidemiological records which go far to establish :

(*a*) that the epidemiological features of the cycle of years within which influenza explodes are different from those of the influenza-free cycles ;

(*b*) that, preceding epidemic influenza, there is often a rise in general morbidity of the population, an 'epidemic

constitution' develops favourable to influenza, there are early though often mild and typical forerunners of the disease, and parallel or allied clinical maladies are seen ;

(*c*) that there are concurrences, similarities and inter-relationships between outbreaks of cerebro-spinal fever, poliomyelitis and outbreaks of influenza, bronchitis and pneumonia."

Before leaving the crest of the great 1918-19 prevalence, the London Annual Reports of 1919 and 1920 (25i, 4 and 5) may be referred to as giving brief consideration—the former (pp. 23-27) to other contemporary epidemiological writings, to recent work on ultravisible viruses and to experiments made to determine the mode of spread of influenza ; the latter to a detailed account (pp. 28-31) of prevalences of epidemic diseases in certain institutions, where they were notified in 1917 and 1918 as outbreaks of dysentery and typhoid fever ; but these prevalences were suspected at the time to be, and in the light of subsequent happenings almost certainly were, in the main, examples of gastro-intestinal influenza. (See also "The Influenzal Constitution" (25n, p. 71).)

THE TRAILERS FOLLOWING THE GREAT PANDEMIC OF 1918-19.

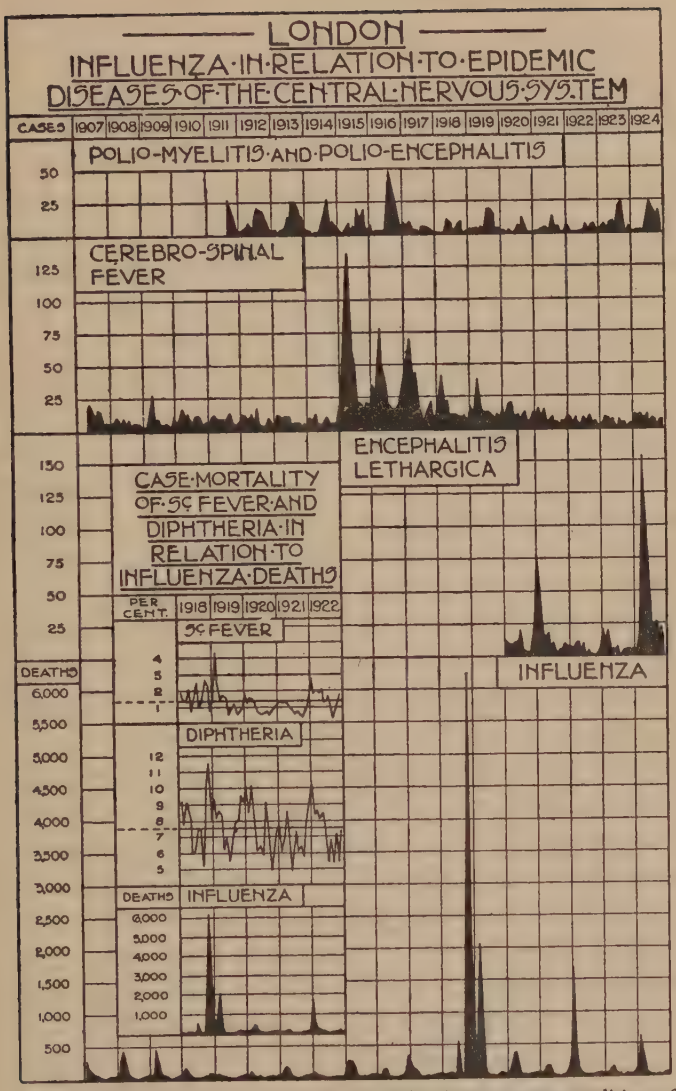
Account of the developments recorded year by year, can perhaps best be given by submitting salient points referred to in the London Annual Reports (25i). That of 1920 (25i, 6) gives a description of trailers of nervous type, particular attention being devoted to *Encephalitis*

lethargica. The Report of 1921 (25i, 7) continues this record, and refers (p. 45) to cases in London and in Manchester in which "differential diagnosis between mild scarlet fever and mild influenza was not clear." The Report of 1922 makes mention of a like difficulty in Minnesota, and refers also to difficulties experienced in Galveston, Texas, in distinguishing *Dengue* from Influenza; this Report also discusses periodicity in influenza. The Report of 1923 recurs to the subject of dengue—notes that "Dr. Shuman of Los Angeles (54) has recently observed that 'In any modern textbook in which dengue is written up, if the reader supplies influenza for dengue the subject-matter will not have to be greatly changed.'" Moreover, comment is made in the London Report of 1923, (25i, 8, p. 23) on the fact, that "Between July and October, 1923, a considerable prevalence of *Dengue* in Calcutta, and, indeed, throughout India, coincided in time of occurrence with a recrudescence in London of influenza." Apropos of cerebro-spinal prevalences of influenza, it is further noted that "a *Heine-Medin outbreak* occurred last year in Tübingen" (Med. Science, Oct., 1923, p. 27). "The principal feature," it is stated, "of the epidemic was the influenza-like nature of the initial symptoms." . . . "In abortive cases the diagnosis from influenza was impossible." The London Report (pp. 24 and 25) also gives a detailed account of the behaviour of encephalitis lethargica in London, and comments upon reports from America (Jour. Amer. Med. Assoc., March 1st, 1924) to the effect that "This peculiar malady appears to change its symptoms from

year to year. In 1919 and 1920 the predominating symptoms were drowsiness, ophthalmoplegia, etc. . . . In 1921 they were profound toxæmia, cranial nerve palsies, delirium, headaches, and neuralgic pains in the limbs." In 1923, at least in Minnesota, there seemed to be an entirely new set of symptoms. "In one group of cases myoclonic twitches of the face, limbs or trunk predominated, and in another group of cases mental confusion with headaches." The London Report (pp. 28-29) also alludes to the phenomena of immunity in the diseases of the influenzal group, and makes some suggestions as to the explanation of the varying phases in influenza. On pp. 32 and 33, further reasons are given for concluding that *gastro-intestinal influenza* accounted for certain outbreaks simulating dysentery and typhoid fever in the London mental hospitals.

The diagram shows the time relationships of the great influenzas and the prevalences of epidemic diseases of the nervous system forming part of their "setting." These cerebro-spinal precursors and trailers preceded and followed the great influenzas of 1918-19, much as comatose fevers preceded and followed the great influenzas of earlier centuries. The diagram also exhibits (as an inset) the raised case-mortalities in diphtheria and scarlet fever noted at the times of prevalence of influenza.

The Annual Report for 1924 (25i, 9) discusses types of nervous prevalences associated with influenza since 1918, with special reference to encephalitis lethargica, and (pp. 109-110) to the after-effects thereof. The Report alludes (p. 23) to the opinion now beginning



The inset diagram, below and to the left, shows case-mortalities of scarlet fever and diphtheria in relation to influenza deaths.

to be entertained that it is " In the *varying after-results*" that encephalitis lethargica differs so markedly from earlier forms of encephalitis. It is pointed out, however, that " Cameron, from the clinical point of view, and Shrubsall from that of the school medical officer, have made it clear that many of these cases are merely exaggerated examples of the ' difficult child,' and that firm and judicious handling brings about marked improvement." The Report continues, " It would be impossible to prove that the particular type of difficult child in question had only been met with in recent years; indeed, it is recognised that children suffering from chorea not infrequently develop disturbances of moral behaviour, and in these considerations justification may perhaps be found for the view that ' this disease is not new.' It may be added that in Sydenham's ' New Disease ' of 1685, the mischief affected the brain in numerous instances; Willis's influenzas of 1657-59 were preceded and followed by fevers ' infestous to the brain and nervous stock '; Sir George Savage(53) in our own day has told how increase in insanity followed upon the influenza of the ' nineties '; and even in the English Sweats of four centuries ago we read how sufferers beat their heads against walls and threw themselves into the water. All those who accept without question the fact that the primary attack in influenza is upon the cerebro-spinal nervous system, and who hold that an epidemic must be judged by its epidemiological characters, as well as by the symptoms exhibited in individual cases, will regard these recurrences of particular associations, described

again and again during the last five centuries, and yet once more in the present century, as illustrations of the truth that there is an abiding unity of influenza among all its seeming diversities."

The 1924 Report further (p. 25), discusses Dr. McNalty's analysis of the differences between encephalitis lethargica and poliomyelitis; Dr. Cadham's account of recent *epidemics of hiccough* in Winnipeg; the "New Disease" of Japan, the symptoms of which closely resembled those of encephalitis lethargica though the usual eye symptoms were absent; and the fatal poliomyelitis outbreaks of Iceland and of Queensland. It urges (p. 26) that "The time has come when an *influence* or *virus* must be invoked in explanation of the phenomena—a virus primarily attacking with special severity now one and now another portion of the cerebro-spinal nervous system, but capable also, at other times and on other occasions, of working mischief in other systems (gastro-intestinal or pulmonary) of the human body. The idea that such a virus or influence is at work is at once grasped when the great epidemics are studied, for the truth cannot fail to be recognised in connection with 'posting prevalences' which sweep across the civilised world at intervals of twenty or thirty years; the mark of the blow directed at the cerebro-spinal nervous system is perhaps quite as unmistakably set upon the 'trailers,' those lesser epidemics following like ripples upon the falling waves of the pandemic prevalences; and, as is now becoming apparent, even in the sporadic cases of illness occurring in the troughs of the great waves,

it is possible to guess at the nature of the influence at work.

"The diagnostician must, of course always have in mind the time and space relationships of the particular sufferer under examination, and must look for such clues as may be to hand on careful consideration of symptoms and the previous disease history. This can be quite successfully accomplished, in some instances, for it is a well known fact that particular individuals are apt to react again and again to influenza, some years after or before the occurrence of a widespread epidemic prevalence.

"From the epidemiological standpoint it is clear, then, that the epidemics affecting the central nervous system which have been under consideration, all stand in close relationship to one another and to influenza. They are none of them 'new diseases,' though it must be agreed that in order to find parallel instances to the recently observed vagaries of encephalitis lethargica we have to hark right away back for a number of years. Dr. Crookshank has told us of the "Nona" of 1889-1890 (10a, 7), and of the choreas and schlafsuchts of still earlier times, and my colleague, Dr. C. J. Thomas, recollects seeing cases with lethargy and ocular palsies in London in 1899-1900. The question has now, therefore, to be considered whether epidemics, attacking different portions of the cerebro-spinal nervous system, and therefore producing widely differing symptom complexes, may be due to related viruses, or even to some one virus, producing effects of varying character, when operating upon communities exhibiting differing degrees of resistance to

infection, or living under differing climatic or social conditions. Thus, at one time and in one place, the virus more particularly affects the grey matter in the cortex or the mid-brain, at another time and in another place, the meninges, or the anterior cornua of the grey matter of the spinal cord, or poisons even the nerves themselves. It would appear, in fact, that the circle is now completed and we are back again at a starting-point—at the Heine-Medin concept of an epidemic disease affecting one or another part of the nervous system—which was roughed out in Scandinavia and Germany forty or more years ago; though it must be remembered that, under that conception, while the cases occurring in the "trailers" were grouped together, the latter were not at the same time roped in with the "pandemics" as forming part and parcel of an influenzal constitution.

"It is, at any rate, plain, in the light of recent events, that no clear line of demarcation can be drawn between epidemic cerebro-spinal meningitis and the posterior basic meningitis of small children; between epidemic hiccough and encephalitis lethargica; between polio-myelitis and polio-encephalitis; between the form of polio-encephalitis which has been described as epidemic stupor and encephalitis lethargica; between the various types of the above diseases encountered in Melton Mowbray, Devon, Cornwall, London, Sweden and America. The time seems, therefore, to be ripe for a little synthesis, now that analysis has brought matters to this impasse."

Crookshank's reminder may be quoted here (10a, 8). He says: "It is only with regard to *cases* (not *epidemics* or *outbreaks*) that the suggestion of a protean malady is entertained. Yet, as a matter of fact, always in each apparently autonomous prevalence are all 'types' represented, and for each type in each prevalence is there somewhere some prevalence represented by predominance of that type."

The 1924 Report goes on once again to compare and contrast (p. 28) the pandemic prevalences—with rapid transference of infection from case to case, stress of the attack upon the nervous system, high percentage of recoveries and frequency of relapses and sequelæ—and the trailers, marked by less rapid transference of infection, localisation of attack upon some special system (pulmonary, gastro-intestinal or nervous), high case-mortality and protracted convalescence. It continues:—

"The fact that the pandemic prevalences stand in such marked contrast with neighbouring trailer prevalences has been held of late years to imply that the germ of influenza must be peculiarly subject to variation just before and after the pandemic outbreaks. In the pandemic the infecting agent is presumably derived as a rule from early cases of illness, it multiplies rapidly, produces toxins which affect the central nervous system by 'shock attack,' and then leaves the individual sufferer with fairly complete immunity, so far, that is, as liability to experience a second 'shock attack' is concerned. In the trailer, on the other hand, the infecting agent is more deliberate, possibly prone to assume 'resting forms,' and

apt to activate various secondary or associated organisms, pneumococci, streptococci, meningococci, etc. . . .

"The post-pandemic trailers . . . become less fatal and less frequent; in the trough between two pandemics the organisms (are) comparatively feeble and trailers of a mild type occur at prolonged intervals of time; finally, as the appointed occurrence of the pandemic phase again approaches, the trailers occur more frequently and gradually assume greater severity. This scheme of things may be further illustrated as follows: The 'primary influence' concerned in producing influenza, following upon biological change, which it has been assumed occurs towards the close of a pandemic period, obviously begins to contend with difficulty in spreading through the increasingly immunised community; it thus resembles a car which has been moving rapidly on high gear and now has to drop into low gear and move more slowly. After 10-15 years travelling upon this upward ascent (during which time the extent of immunisation of the population as a whole, against the various manifestations of influenza, is steadily growing) the climb gradually begins to lessen in severity; but for another 10 or 15 years (during which the susceptibility of the population slowly increases) the journey has still to continue on low gear. Then as the community, owing to the comparative infrequency of prevalence of one or other of the diseases of the influenzal group, becomes more and more susceptible, the rapidity of transference of infection shows increase and, when the time for pandemic prevalence again arrives, change into high gear is once more affected

and world-wide spread of influenza in pandemic phase again results."

The closing paragraphs of this section of the report (pp. 30-32) are concerned with study of *periodicity* (as examined by Dr. Brownlee and Mr. Spear), in connection with the foregoing hypothesis relating to the form of the epidemic wave. This examination is summed up in the following statement.

"The clue in fact for threading a way through the maze of the varying periodicities seems to be to recognise a normal annual interval; this may be varied by intervals of about $\frac{2}{3}$ and $\frac{1}{3}$ of a year, making together periods of 2 years; while near the pandemic itself epidemics at quite short intervals may be encountered. Study of periodogram results on the whole confirms this way of looking at the question and thus supports the theory of three predominating factors: a '*climatic*' *factor* favouring the normal annual periodicity; a *varying* '*immunisation*' *factor*, tending to the shortening of intervals, on either side of the mid-period (of long intervals) between pandemic and pandemic; and then, thirdly, a factor causing speeding up in years near to the pandemic times—this last-named phenomenon (especially when the variation of type, which accompanies the merging of the trailer into the pandemic, is borne in mind) may be suspected to be due to a *recurring* '*biological change of state*' *factor*. It must be realised that during all these variations, and throughout the years stretching from pandemic to pandemic, influenza, in one or other of its phases, is ever present, perennially smouldering,

'*endemic*,' but only producing epidemics at times when the balance of conditions as regards immunisation, and as regards climate and season, are such as to permit of more or less widely spreading conflagration."

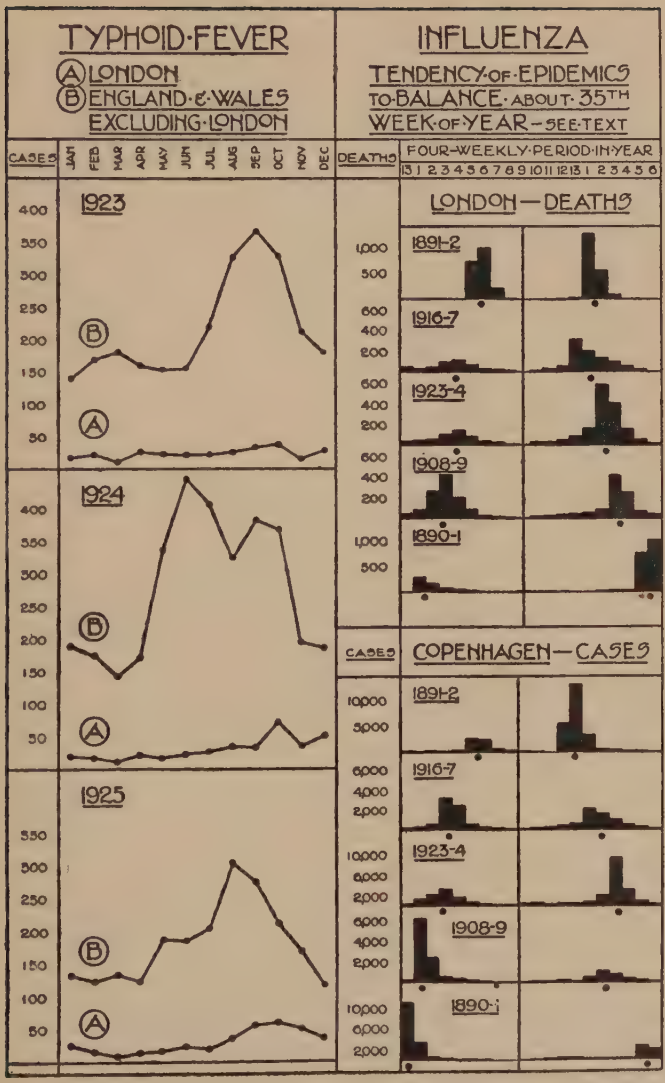
The Annual Report for 1925 contains (p. 106) a comprehensive report on *encephalitis lethargica*, in the course of which it is pointed out that the case-incidence of cerebro-spinal fever, " which was very high in the years 1915-1917, has fallen materially since that date, so much so as to raise some doubt as to whether certain cases, which might in former years have been called cerebro-spinal fever, may not have latterly been termed encephalitis lethargica." It is added that " The outbreak of these diseases has borne a distinct relation in point of time to that of influenza. Some forms of influenza have given rise to nervous symptoms of a similar character, though milder in degree and of shorter duration than those noted in epidemic encephalitis. For example, somnolence and, later, irritability were commonly observed in 1924, while double vision occurred occasionally. The infectivity of encephalitis is apparently of a very low order, if attention be paid to cases only showing nervous symptoms. It is, however, possible that the infection may be conveyed by those in whom the disease takes some other form, or by the apparently healthy."

The Report also deals with the sequelæ of encephalitis lethargica and with the relation of the symptoms and sequelæ of this disease to those of other disorders of children. It further contains (p. 32) references to Dr. Chalmers' Watsonian lectures on " The epidemic diseases

of the central nervous system"; and the similarity of experience, in these epidemics, as studied epidemiologically in Glasgow and in London, certainly seems to confirm Sydenham's advice (M.O., V, vi, 3), "If any one ask how he is to fish out the species of a continued fever let him choose for his field of observation some large and populous place." This Report also contains (p. 34) an important note by Mr. B. E. Spear on the balanced incidence of influenza about the thirty-fifth week (see accompanying Diagram and 56b).

Finally, in a discussion (on p. 41 of the Report) on the *abnormal autumnal incidence of typhoid fever*, reference is made to anomalous outbreaks of typhoid fever, outside London, as well as in the county itself. The Diagram contrasts the seasonal incidence manifested by typhoid fever in London and in England and Wales. London had ceased to show a marked autumnal wave upon the outbreak of the Great War, and some of the aberrant prevalences in England and Wales during 1923-25 may perhaps be attributable to confusion between typhoid fever and gastro-intestinal influenza.

On reviewing the epidemiology of the years 1915-25, the dominating prevalences are seen to have been cerebro-spinal, pulmonary and gastro-intestinal types of influenza —among the early precursors and the late trailers comatose fevers and gastro-intestinal outbreaks hold the field, in the centre of the picture are the universal fever of June-July and the fatal coughs and catarrhs of Oct.-Nov., 1918. It will be seen later that these happenings almost exactly repeat those of the years round about


TYPHOID FEVER
(A) LONDON
(B) ENGLAND & WALES EXCLUDING LONDON
CASES
JAN FEB MAR APR MAY JUN JUL AUG SEP OCT NOV DEC
1923
1924
1925
INFLUENZA
TENDENCY OF EPIDEMICS TO BALANCE ABOUT 35TH WEEK OF YEAR – SEE TEXT
DEATHS
FOUR-WEEKLY PERIOD IN YEAR
LONDON — DEATHS
1891-2
1916-7
1923-4
1908-9
1890-1
CASES
COPENHAGEN — CASES
1891-2
1916-7
1923-4
1908-9
1890-1

1675; indeed, it was to them that the words already quoted, which were used by Sydenham two hundred and fifty years ago in speaking of his fifth constitution, were applied. He said, the constitution "has been exceedingly anomalous and irregular and all the diseases which have originated from it have been the same."

CHAPTER II

EPIDEMICS IN LONDON IN THE TIME OF SYDENHAM AND AT THE PRESENT DAY

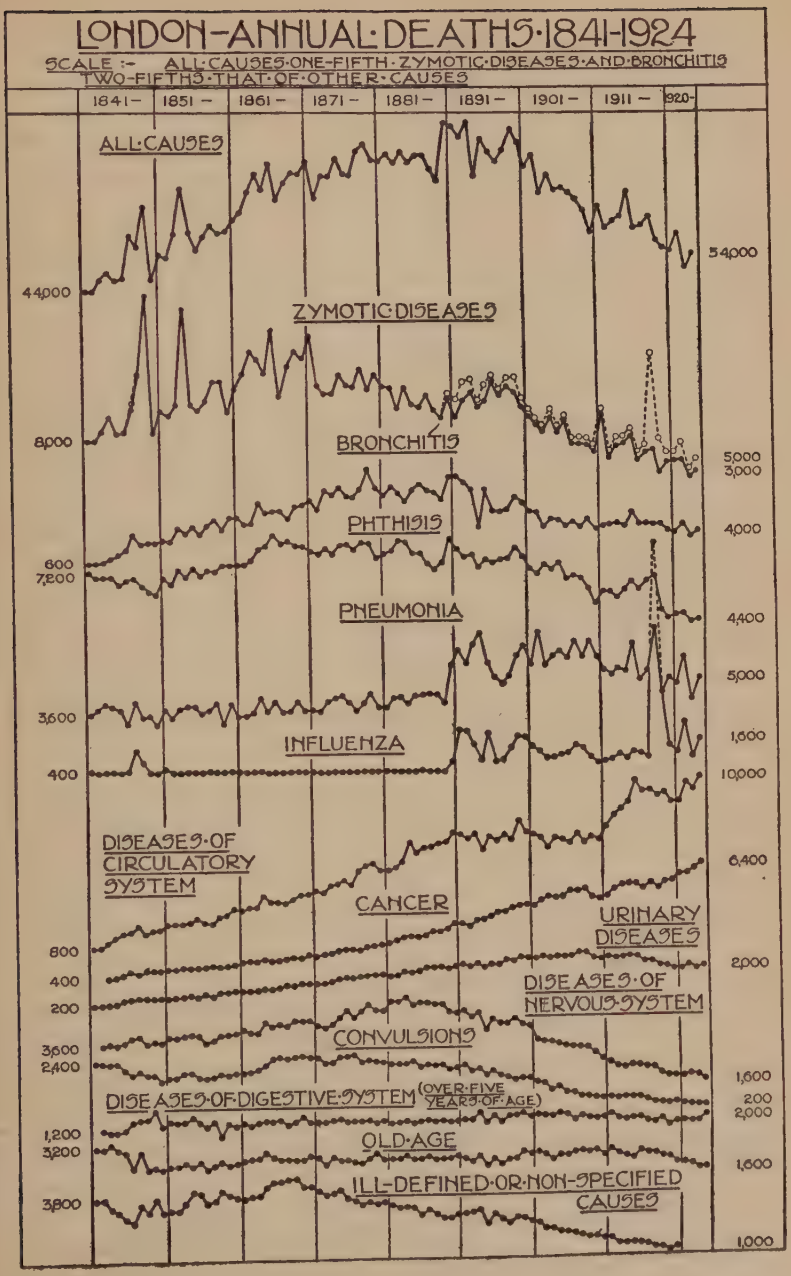
Some Contrasts and Some Resemblances

In Epidemiology the older or Hippocratic method "took account of gradations, modifications, affinities." It may be likened, Creighton says, to the mason's rule of lead of Lesbos, which could be adapted to the form of irregular stones, and was thus (Aristotle. *Nic. Ethics*, 5.10.7) emblematic of the special ordinances appropriately applicable in special cases. During the last hundred years the great advance in knowledge, of morbid anatomy and histology, and of bacteriology, has brought about a radical change in the clinical and epidemiological outlook. The older method of studying epidemics envisaged a wood, the new knowledge has caused that wood to be hidden by trees.

"Sydenham," Creighton tells us, "was the great exponent of the Hippocratic method, but even he sketched out another method of describing diseases, as if they were species or natural kinds" (M.O., I, ii, 18 and 19). But "He did no more than indicate this analogy, at the same time declining to put it into practice." He advised

great caution in dealing with symptoms, noting that "No botanist takes the bites of a caterpillar as a characteristic of a leaf of sage"; moreover, following this up, he at length came to regard epidemic disease as an epiphenomenon, the outcome of interaction between a virus and the humours of the body. (Pref. to 3rd edn. of M.O., 7-11 and 18-19 and M.O., I, i, 6). He began with one "continued fever," and then described another, and a third; but, as his outlook widened, he, who had at first been alert to detect differences, was impelled, by his experiences in 1673-6 and in later years, to recognise "gradations, modifications and affinities." It will be seen presently that the same change in mental attitude was observed in those who studied the prevalences of the "nineties" and, more recently still, those of the years 1915-25. Indeed, the Ministry of Health Report of 1920 (38a) states that "Various clinical forms of infective disease tend to assume a generic type and to prevail before and after an epidemic of influenza." The time seems ripe, therefore, for taking stock of these modern "settings" of epidemics and comparing them with Sydenham's Constitutions, particularly noting his Constitution of 1673-76.

The Diagram showing London deaths in registration times suggests that the part played by fashion in the use of nomenclature has played many tricks with the records. Note as a conspicuous instance of this the erratic behaviour of influenza and pneumonia and in less degree of bronchitis. Note, too, the great apparent increases in diseases of the circulatory system and in cancer.


LONDON-ANNUAL DEATHS 1841-1924
SCALE :- ALL CAUSES ONE-FIFTH ZYMOTIC DISEASES AND BRONCHITIS TWO-FIFTHS THAT OF OTHER CAUSES
1841 – 1851 – 1861 – 1871 – 1881 – 1891 – 1901 – 1911 – 1920-
ALL CAUSES
44,000
54,000
ZYMOTIC DISEASES
8,000
BRONCHITIS
5,000
3,000
PHTHISIS
4,000
600
7,200
PNEUMONIA
4,400
5,000
3,600
INFLUENZA
1,600
400
10,000
DISEASES OF CIRCULATORY SYSTEM
6,400
CANCER
URINARY DISEASES
800
2,000
400
DISEASES OF NERVOUS SYSTEM
200
CONVULSIONS
3,600
2,400
1,600
DISEASES OF DIGESTIVE SYSTEM (OVER FIVE YEARS OF AGE)
200
2,000
1,200
3,200
OLD AGE
1,600
ILL-DEFINED OR NON-SPECIFIED CAUSES
3,800
1,000

There are two main difficulties to be reckoned with in comparing epidemics of earlier years with those of the present day. In the first place, as Professor Greenwood has remarked, we must *not* suppose "that because a writer of the seventeenth or eighteenth century uses words which, used as *we* use words, seem nonsensical, he was therefore writing nonsense; a great deal more is needed than a mere study of the texts (of the earlier writers), it is necessary to acquire a new sense of intellectual values by reading the books . . . with the teaching of which the older epidemiologists were saturated." We may then begin to appreciate that when Sydenham distinguishes between "epidemics" and "intercurrents" he means something by it, even though, once in a while, he speaks, as Dr. Crookshank points out, of an intercurrent assuming an "epidemic character" (58a, M.O., VI, i, 3). Again, when he refers to intermittents losing their intermittency and becoming changed into continued fevers (V, vi, 2), he is describing that which he has experienced and "knows right well." Prof. Boycott, as has been seen, holds the ideal bacteriologist to be the man who studies bacteria for love of the germs themselves. Sydenham approached the study of epidemic diseases in this spirit and he had the great advantage, denied to most of us nowadays, of being able to regard them mainly from an epidemiological point of view. He noted differences, but did not ignore affinities. He sees epidemics "steadily, and sees them whole."

And secondly, as has been often said, we are at a great disadvantage in setting against our modern death and

notification rates, the statements of older writers (Sydenham, for example) that such and such a disease "prevailed a little," "became epidemic," "caused many deaths," and the like. In Sydenham's case, however, we can obtain a certain amount of help from the London Bills of Mortality; though in dealing with "continued fever," "intermittents," etc., the nomenclature difficulty is bound to arise.

Assuming, however, that there is some continuity in epidemic diseases, the Bills may be invoked to help us in making comparison between the extent of prevalence of "influenza," "typhus," "pneumonia," etc., to-day, and that of corresponding epidemic diseases which, presumably lie hidden under descriptions of "continued fever," "intermittents," "pleurisy," etc., in the writings of Sydenham, Willis, Whitmore, Morley, Molyneux and Morton.

Dr. Farr (16) gives a Table showing deaths and death-rates (from twenty classes of disease per 100,000 living), in 1660-79, which can be compared, as follows, with those of recent years.

I The death-rate (all causes) in 1660-79 was more than four times that in 1901-10.

II The infantile mortality was perhaps even more than four times that in 1901-10.

III The excessive rates for all ages, in 1660-79 were mainly ascribed to "plague," "consumption," "dysentery," "fevers," and "small pox."

> The remaining deaths constitute about one-fourth of the total, and the chief items appearing are "dropsy," "old age and bedridden," "childbed and miscarriage," "surfeit and cholera" and "other diseases." "Casualties" yield rather less than one per cent. of the total deaths. "Bronchitis," "pneumonia," "influenza," and "cancer" are not even represented in Farr's Table.

There must be a considerable error in the rates for the earlier period, owing to uncertainty as to the size of the population upon which they are based. We are doubtless on safer ground in considering deaths rather than death-rates and, doing this, it transpires that the "searchers" included about one-tenth of the total deaths under "fevers." Plague, small-pox and measles, however, are returned separately; if they be also counted as "fevers" that heading would comprise more than one-fourth of the deaths from "all causes."

And now as to Sydenham's view. Dr. Payne (46) says Sydenham estimated that "fevers made up two-thirds of medicine," and, he adds, "the same class of maladies, called in official returns, "zymotic diseases," are credited with only one-tenth of the total mortality from all causes . . . the difference is enormous." Again, Dr. Comrie (8) writes: "He (Sydenham) estimated that fevers made up two-thirds of medical practice." The word estimate, in these days of statistics, is apt to convey an impression of precision which was clearly

not present in the mind of Sydenham. His exact statements are as follows :—

I In the letter to Dr. Cole (58b, para. 59) speaking of hysteria, he remarks that " fevers with their attendants constitute two-thirds of the diseases to which mankind are liable."

II In the letter to Dr. Brady (58b, para. 52) he incidentally notes " fevers form two-thirds of medicine."

III In the *Tractate on Dropsy* (58b, para. 21), speaking of acute diseases, he says, " two-thirds are acute."

IV In the *Medical Observations* (58a, VI, vii, 10) we read, " Many die by violent deaths ; but with the exception of these, two-thirds of our race die of fevers."

It is obvious from these statements, first, that Sydenham was giving merely a rough guess, and second that in thinking of fevers he cast his net far more widely than the " searchers " did ; thus, in making our comparisons between the 1660-79 figures, and those of 1901-10 we must take " fevers " as including much more than the " principal zymotic diseases " of to-day.

In order to clear up the difference between Sydenham and the " searchers " appeal must be made to modern clinical experts. Sir William Jenner (32), who stands nearer to Sydenham than the present generation of clinicians, recognised *three* continued fevers, and he said

(32,3) that the diseases, most likely to be mistaken for them, were pneumonia, intracranial inflammations, febricula, pyogenic fever, and acute tuberculosis. (Febricula (32, 4) he regarded as a non-contagious and sporadic affection, which, however, "now and then reigned as an epidemic.") Comment has been made elsewhere (250) on the curious omission from Sir Wm. Jenner's list, of influenza, mention of which is made only once in his book (p. 321) in connection with diagnosis as between it and "latent typhoid fever."

An authority nearer to the present time, Dr. Payne (46), observed that "The most disappointing feature in Sydenham's accounts of fevers is that, notwithstanding their minuteness, it is hard to be certain what species of fever, as now understood, he is describing in any particular year." . . . "As it is, such an identification is difficult, and in the end uncertain." He notes, however, that Sydenham speaks (58a, M.O., VI) "of a number of acute diseases, not generally called fevers, and anticipates very modern views respecting these diseases. He refused to recognise them as *local* diseases, originating in the organs affected. With regard to pleurisy and pneumonia, for instance, he insists that they are due to a general inflammation of the blood, which causes the affection of the organs (see also V, v, 1-3). So with Erysipelas, Rheumatism and Quinsy. He regarded them all as *fevers to begin with*, not as feverish diseases arising from the local conditions."

A present-day clinician, with almost unique experience of fevers, and one who knows his Sydenham

(Dr. Goodall) writes, " From a careful perusal of his writings, I have no doubt that he saw smallpox, chicken-pox, measles, scarlet fever, plague, typhus, relapsing fever, enteric fever, dysentery, autumnal diarrhœa, ague, influenza, cerebro-spinal fever and epidemic encephalitis " (21 b). If we add to this list the five " local diseases " mentioned by Dr. Payne (to which inclusion Dr. Goodall would doubtless assent) we have a near approach, it may be submitted, to Sydenham's " fevers."

But while modern authorities are agreed in accepting some such connotation as this, the question was looked at from a different angle, by an almost contemporary critic, Dr. John Freind (20). After remarking upon the identity of certain fevers, described in the Third Book of The Epidemics of Hippocrates, with those in the First Book, and upon their being referable, therefore, to the Constitution of the Air of which account is there given, he goes on to say that " Fevers are almost the only diseases which are common to all Nations and to all Ages." He then adds, " Those very fevers which Sydenham explains as distinct species, according to the various temperature of the seasons, do not differ much from one another. For, if perhaps you should except the *petechial*, they differ rather in *degree* than in *kind*. There hardly ever appeared a fever in any season, where the signs so constantly answered one another, that those which you found collected in one person, should unite after the same manner in another : however, upon this account you would not deny their labouring under the same distemper. And that this is true, his method of

treating these diseases may be alleged as a proof: for I observe that almost the same method of cure is accommodated to all the *eight* species of fevers, which are distinguished by this gentleman. So far was he from proceeding upon different methods of cure. He tells us, indeed, *that the continual fevers were so widely different*, that the same method which relieved the patients at the beginning of the year, towards the end of it might possibly carry them off: but, if we should consider the method which this writer pursued in the curing of these fevers (of a kind as he imagined so very dissimilar) and in which he greatly excelled, we shall find no appearance at all of this matter. So superfluous for the most part is every over-nice distinction, and of so little service to the students in physic especially, that it rather leads them into an error, inasmuch as they falsely imagine, when they find any certain peculiar sign affixed to any distemper, that the method of cure must in like manner be particular."

Two questions seem to arise here: the first as to fevers at the beginning and at the end of the year, and their treatment. Concerning this there cannot be any dispute. Some epidemics prevail in the spring and others in the autumn; and Sydenham, of course, clearly set out his view on this matter in his account of vernal and autumnal fevers. He has shown, moreover, both in this connection, and in distinguishing between "epidemic fevers" and "intercurrents," that correctness in diagnosis may exercise very important influence upon the question of treatment. (58b. Letter to Dr. Brady, paras 52 and 53.)

But the most interesting point in Freind's criticism is the alleged application, by Sydenham, of "almost the same method of cure to all the eight species" of stationary fevers. This criticism was referred to by Creighton (II, 27 Note), and has also been noted by Professor Greenwood (24c). When thus cited, there may be said of it, as was written of the truth preached in "The Deserted Village," that "It prevails with double sway, allures to brighter worlds and leads the way." It gives, in point of fact, expression to *the* difficulty, that which again and again troubled Sydenham himself. It is one which he expressly comments upon in the Dedicatory Epistle (*vide infra*), glances at in the Preface to the Third Edition (*passim*), and in V, vi, 6 of the M.O.; and these remarks, as will be seen later (pp. 91-96 and 143-145) must be read with the Postscript to the Tractate on Dropsy and with the account of the setting of the "new fever" in Schedula Monitoria, I. In the Dedicatory Epistle to the third Edn. of the M.O. (58a, p.4) he explains that his growing experience of fevers had shown him that, in thinking, in earlier days, that he could forge "a Delphic sword, in the shape of some methodus medendi, which should meet all cases," (he) "had opened his eyes only to get them filled with dust"; and he goes on to lament that those who charged him with what now seemed inconsistency, should "deem themselves injured when others proclaim new facts of which they themselves had no previous knowledge." (See also Processus Integri, chaps. 2-5.)

Professor Greenwood (l.c. p. 75), smilingly hints that

some enthusiast (stimulated by Freind's criticism) might be tempted to generalise further still and "perhaps, to wonder whether Epidemiology as a whole were not a series of variations upon the theme Influenza." But this of course would involve reducing the eight stationary fevers to one, and would take us right back to the youngest Sydenham of all, to the days when he was starting practice, at which time, he says, "I had no notion that any second form of fever was to be found in rerum natura" (M.O., I, iii, 8; see also Sched. Mon. I, 46). The older Sydenham was prepared to generalise up to a point but, as a matter of fact, he only assigned his "standard fever" the leading rôle in one of his Constitutions, giving it less prominence in four or five others, while it is almost lost to view in the remaining two or three.

Creighton's testimony is to a like effect. The laying of stress upon "gradations, modifications, affinities," is primarily applied by him (II, vii, 678) to Scarlet Fever and Diphtheria; and then, later (II, viii, 747), to Diarrhœa and Dysentery; it operates, however, in influenza, when he styles his Chap. III, Vol. 2, "Influenzas and Epidemic Agues," for the reason that "they can hardly be separated in the earlier part of the history"; and then again, following Noah Webster, he says, "Influenza is the crux of Epidemiology" (II, iii, 405). It is none the less clear that he is only prepared to generalise up to a point.

It is time, however, to come to closer quarters with Sydenham's Constitutions.

The conception of a constitution was derived from Hippocrates, but in Sydenham's mind it underwent a

remarkable transformation. The comments of Dr. Adams the editor and expositor of Hippocrates (28), upon the cases described at the end of Book I of the Epidemics, give some of the essential characters of the Hippocratic method. He says, " It must strike everyone as a singular feature in these cases that the lineaments of a particular disease are seldom to be recognised, and this perhaps may be regarded as a proof of the faithfulness with which they have been copied from Nature. In short, we here recognise the features of disease in the concrete and not in the abstract, and is not this what we should expect in all copies from Nature ? " . . . " It is commonly supposed that the physician on examining the characteristic features of any case, should have no difficulty in pronouncing that it is *pleuritis*, for example, or *pneumonia*, or the like, but how often does it happen that the complaint in question is an aggregation of symptoms, produced by peculiarities of constitution and incidental circumstances, which, taken together, constitute an *ensemble*, which does not well admit of being referred to any one of the general forms of disease described in our nosological systems ? " Later (l.c. page 384), Dr. Adams says, " Indeed it appears to me to be too much the practice of the profession as well as the public to imagine to themselves a certain type or ideal of every disease, and when they do not recognise the exact characters which they fancy it represents, they immediately set down such cases as constituting an entirely different disease."

Turning now to Sydenham, he, it would seem, hit upon the idea of describing epidemics as Hippocrates had

described cases (see Epistle Dedicatory to 3rd Edn. of M.O., p. 4). He conceived them to arise "partly from the particles of the atmosphere and partly from the different fermentations and putrefactions of the humours." (M.O., I, i, 1). The former "taint the human frame, but they depend upon the peculiar crases of our blood and humours only so far as these occult atmospheric influences have made an impression on them." (M.O., I, i, 6) . . . "The species of disease depend upon the humours that engender them." (Pref. to 3rd Edn. of M.O., par. 19.) He described five constitutions, each of which takes "the melancholy characteristic of some proper and peculiar form of fever" (its stationary fever). He utilises these fevers as his clues and instead of "calling them by names descriptive of changes impressed upon the blood, or else from some other palpable symptom"—on which principle they would be styled *putrid*, *petechial*, *malignant*, etc., he names them "from the character of the constitution prevalent at the time of their appearance." (M.O., I, ii, 13.)

In addition to the five constitutions of the Medical Observations, he describes two more in a letter to Dr. Brady, and finally (Sched. Mon. I) a later one still. There are available, moreover, descriptions of two closely associated constitutions, one immediately preceding Sydenham's first constitution (by Willis and Whitmore) and the other following Sydenham's last constitution, from the hands of Molyneux and Harris. These ten Constitutions will be taken in order. (See Table on opposite page.)

TABLE OF CONSTITUTIONS.

Including three Influenzas (I, VI and X), the Five Constitutions of the "Medical Observations" (II, III, IV, V and VI, and three later Constitutions (VII, VIII and IX).)

Constitutions.			Setting of Influenzas.		Schema for Whole Series.
I			1657 to 1659	Universal Fever of Willis in a "setting" of Protean Fevers	Precursors Influenza Trailers
II	1661 to 1664	Intermittent with Continued Fever			Intermittents
III	1665 to 1666	Plague with Pestilential Fever			Standard Fevers of the trough between the Great Waves
IV	1667 to 1669	Small Pox with Variolous Fever			
V	1669 to 1672	Dysentery with Dysenteric Fever			Intermittents
VI	1673 to 1676	Epidemic Coughs with Comatose Fevers	1674 to 1676	Universal Fever in a "setting" of Comatose Fevers.	Precursors Influenza Trailers
VII	1678 to 1680	Intermittent with Continued Fever			Intermittents
VIII	1681 to 1684	Depuratory Fevers or "Dregs of the Intermittents"			Standard Fevers of the trough between the Great Waves
IX	1685 to 1686	A New Fever			Intermittents
X			1688	Fever of Molyneux and Harris	Precursors Influenza Trailers

I. *Willis's Constitution of* 1657-59. His *first* prevalence was a " brain fever " reminding us of the cerebrospinal fever of 1915, or the encephalitis lethargica of 1918. The *second* came, " as if sent by some blast from the stars " . . . and " laid low many together." Creighton (9b, i, 570) pronounces it an influenza. The *third* resembled the first. " In some, on the first or second day, came little broad and red spots." " The exanthem," says Creighton, " reminds one more of the rash of sweating sickness or dengue, than the spots of typhus." He adds, " The strangest part of these narratives is not the catarrhal influenza . . . but the presence of anomalous fevers, in respect of contagion, spots, pains and other symptoms, like typhus. There are many more experiences of the like kind in the years to follow." Willis (66b) has a later essay on a fever, " chiefly infestous to the brain and nervous stock," occurring in 1661, the year of commencement of Sydenham's first constitution.

II. *Sydenham's Intermittent Constitution with a Continued Fever throughout.* 1661-4. Creighton (9c, i) says, " The epidemic beginning in 1661 was not an ordinary tertian intermittent; no one, save Sydenham, calls it an Intermittent at all, and he qualifies the intermittent character, in quite a drastic manner."

Among symptoms of the " stationary " or continued fever of this constitution described by Sydenham, were, sweatings, frenzies, inflammation of the brain and pleura, cough with tough and viscid phlegm, epistaxis, diarrhœa, hiccough, ileus (presumably appendicitis) and relapses. He

also mentions swelling of the tonsils, hoarseness, hardness of the belly and dropsical swellings. This description is important, for Sydenham regards it as relating to the "Standard fever of Nature," "both on account of the regularity of the method which it employs in promoting the morbific matter (digesting it at its assigned time) and from the fact of its being of all fevers the commonest in respect of its occurrence" (M.O., V, vi, 1 and I, iii, 8).

III. *Constitution of Plague and Pestilential Fever.* 1665-6. Sydenham saw little of the Plague. As regards the Pestilential Fever, he refers to sweating and danger of supervention of brain fever, but he was inclined at first, to distinguish it from "the commoner sort which we have just dealt with," i.e., from the fever of his first constitution (58a, Vol. I, Appx. A., p. 269). A full account of pestilential fever is given by Willis (66a, Chaps. XII-XIV).

IV. *Constitution of Small Pox with a Variolous Fever,* 1667-69. Dr. Goodall (21b) doubts "whether any writer of modern times has added a single important observation to (Sydenham's) admirable and detailed description of small pox." Sydenham describes variolous fever as small pox without the rash; he mentions, however, headache, pain at the pit of the stomach, sweats, occasionally petechiæ, diarrhœa, and brain fever. The main point of distinction between this and the "Standard fever of Nature" seems to be occurrence of salivation, as in small-pox itself.

V. *Constitution of Dysentery and Cholera nostras with a Continued Fever.* 1669-72. The stationary fever here is marked by headache, aphthæ of the mouth and gullet, lethargy, occasional sweatings, ptyalism and gripes. The two last-named symptoms constitute the main differences between this fever and the "standard fever." Sydenham states (IV, i, 5 and 6) that a "tertian ague" was more common in 1671 than he found it at "any other period" since 1661-4. Thus, it appears that "Intermittents" preceded (as we shall see they also followed) the Constitution of 1673-6. The details given (IV, vii, 1, 2 and 17) point to a gastro-intestinal type of prevalence in 1671. In IV, iv, 2, however, we read of a "carus," or lethargy, in 1670-72; so that cerebro-spinal types of fever were also encountered, as was the case, too, in 1661-4 and 1678-80.

VI. *Constitution of Epidemic Coughs with Comatose Fevers.* 1673-76. The stationary fever of this Constitution is described as a comatose fever, for it was apt to develop into lethargies and stupors; in July, 1675, the fever spread its ravages far and wide, sometimes attacking the bowels, sometimes the head (V, i, 5-7); in October and November came a great prevalence of "coughs and catarrhs" . . . . "the fever, however, remained as before" . . . "all the diseases which originated from it have been the same." The sudden attack of July and the widespread pneumonias of October and November (both prevalences occurring in a "setting" of stupors and lethargies), cannot fail to call to mind the influenzas of 1918-19. Sydenham places on record, too, the

" aphonia with stupor," the head " nodding this way or that " (V, ii, 4), " rheumatism," " jaundice " and " metastasis to nerves."

VII. *Return of the Intermittents* (*almost entirely absent since* 1661-4 *; but see remarks under V* (*above*)). 1678-80. This, the first Constitution of the Brady Letter, completes a cycle begun seventeen years previously. Paras 56 and 57 of the Letter, taken together with the evidence, for 1657-8, supplied by Willis, and for 1688-93, supplied by Molyneux, suggest that there were two complete cycles of epidemics (see Table on p. 83). It is clear, moreover, that the two troughs between the three crests (1658, 1675 and 1688), of these epidemic waves were occupied by " Standard fevers," and these again were both preceded and followed by " Intermittents." (See above and also Sch. Mon. I, 46.)

Sydenham assumes that his readers will have in mind, in connection with 1678-80, his earlier descriptions for 1661-4 ; special mention is made, however, of " cramps," " brain fever," and " relapses." Moreover, in 1679, there was an epidemic cough (an " influenza trailer "), associated with " delirium, lethargy, weak and irregular pulse, dry tongue, and red or even livid spots," . . . " the morbific matter drives to the brain, and all things go to wreck and ruin." (58b. Tractate on Dropsy, para. 4. See also Letter to Dr. Brady, paras 54-58.)

VIII. *Depuratory Fevers or Dregs of the Intermittents*, 1681-84. This and the last Constitution might be grouped together ; they occupy a similar place in the cycle 1675-88, to that filled by II, III, IV and V

in the cycle 1658-75. The "Depuratory Fever," Sydenham suspects, will prove identical with that of his *first* constitution (see Letter to Dr. Brady, 56 and S.M., I, 46); moreover (M.O., V, vi, 1) he actually calls this first fever "the depuratory fever." (See also Proc. Int. Cap. II.) An interesting touch is the reference to a common complication of this fever, "rheumatism" of "the muscular parts of the body." (Brady Letter para. 64.)

IX. *Constitution of a New Fever.* 1685-86. The fever, commencing in February, 1685, has already been alluded to on p. 44. Sydenham noted the chills and flushes by turns, the pains in head or joints, the cough and the pain also in the neck and fauces. "The fever was continued, and the patient might determine the fever to the brain, and convert it into a frenzy. Petechiæ were apt to show themselves, and in young and sanguine subjects there might be purple blotches; if the patient were heated, the perspiration would be clammy." Miliary eruptions, relapses, aphthæ, hiccough and iliaca passio, were also mentioned. "If matters were mismanaged, the spirits were wholly thrown into confusion, an inordinate pulse set in, there was a jerking of the limbs, and death took place. Of all the fevers this attacked the brain the most, and could not be detached from it without great trouble." The "setting" of this fever, as was pointed out some years ago (25k) strikingly recalls that of cerebro-spinal fever in 1915, in London.

X. *Molyneux's and Harris's Fevers of* 1688-93. Creighton's opinion (II, 335-9) that the prevalence of

1688, in London and Dublin, was Influenza, is borne out by the rise in the London Bills of Mortality. In 1693 Molyneux describes a trailing epidemic in Dublin, which also left its mark on the London Bills; Rutty (52) also alludes to this. The importance of these brief references is that they complete the descriptions, for London, of the great influenzas of Sydenham's time, by marking the time of occurrence of the widespread influenza of 1688.

The study of these ten Constitutions throws much light upon acute diseases, and especially upon "fevers." It is essential, is the *first* place, to realise that the "Intermittents" or "Agues" which figure so largely have been given (by later writers) a connotation that would have greatly astonished Sydenham himself. Thus, mainly on the strength of Sydenham's use of the word "intermittent," it is frequently remarked that *malarial fever* was common in London in the 17th century, and that the neighbourhood of Pall Mall, where Sydenham resided, being low-lying and marshy, afforded him much opportunity for studying that disease. Creighton has, however, shown that the term "ague" was simply equivalent in Sydenham's time to "acute fever." Moreover, in the Letter to Dr. Brady, when, after absence for some years, "intermittents" were again "scattered here and there," Sydenham reports "that of these the greater part had not attacked residents in London." (58b paras 10 and 11.)

Creighton, discussing Malaria in London, in Traill's Social England (60) says, "Even when ague was a true fever with paroxysms and intermissions, or with relapses,

it was much more rarely the endemic fever of the malarious region, than the ague of one of those strange universal epidemics, which were frequent enough, and sometimes so prolonged over a succession of seasons, as to make the aguish type a common one in practice from year to year—more common of course in one year than another, and sometimes absent for years together, as medical chronologies clearly show."

Creighton (9c, 3) refers to "Ague Curers" and "The Peruvian Bark Controversy," in the seventeenth and early eighteenth centuries. Sydenham, he says, in 1666 spoke guardedly on the use of bark, but in 1675 he set out directions for administering it. It needs, he adds, to be borne in mind that in "Intermittents" the intermittency was often but ill marked, and they were thus apt to become confounded with continued fevers; moreover, they occurred epidemically. He concludes (60, p. 370) "As to London in particular, and the country close to it, we may be sure that malaria had little or no effect on the public health."

In the *second* place, while we clearly distinguish the three outstanding prevalences of 1657-59, 1673-6 and 1688-93, careful study of Sydenham's Constitutions reveals much more than this, for we visualise not merely the wavelets, representing closely related prevalences on either side of the crests of the great influenzas; there are also to be discerned, in the troughs between the great rollers, ripples corresponding to prevalences of fevers in the intervening years. These are the "stationary fevers" of Constitutions II, III, IV, V, VII, VIII and IX, of p. 83, each of them at first described by a name derived

from that of the corresponding Constitution, but most, if not all of them, including fevers which Sydenham later came to regard as examples of what he called "The Standard Fever of Nature." Dr. Greenwood asked (24a, p. 61) "Are we to understand that *the* characteristic product of an epidemic constitution is its stationary fever, that it is in the type of stationary fever that one constitution differs from another?" Dr. Goodall (l.c. p. 70) replied in the affirmative. This reply seems, however, to require slight qualification, as will appear later (see *b* infra.), when it will transpire that the stationary fever (of the Intermittent Constitution of 1678-80), "which ran parallel with the intermittents, easily became converted into an intermittent."

In the *third* place, detailed examination of Sydenham's various writings throws much light upon his views regarding the changes of type manifested by his fevers; the transitions occurring on the crests of the great rollers, those later exhibited in passing on to fevers a little way down the slope of the great waves and again from these last named fevers to the fevers of the troughs, and so on. These transitions may be studied (starting from the crest of the influenza wave of 1675) at four successive removes.

(*a*) *The Transitions observable on the crest of the wave* (1675). Following upon the Comatose Fevers of 1673 and 1674, the fever of 1675, "which had lasted throughout the whole year, spread its ravages far and wide in July. . . As the autumn approached, it attacked the bowels, and exhibited the symptoms of either dysentery or diarrhœa. At times it was unaccompanied by any rash or symptom.

. . . It then attacked the head, rendering the patient heavy and dull. . . Now it was that the fever had the predominance, taking the lead of the other maladies of the year. It must be observed, nevertheless, that as this fever was more inclined to throw off the morbific matter on the bowels, and as it often excited dysentery, and oftener still diarrhœa, it gave rise to the notion that the gripings which did so much mischief arose from these two diseases; whereas, in reality, they were to be imputed to the fever. Everyone, however, who had any practice among the sick, knew the predominance of the fever, and knew also that the aforesaid dysentery and diarrhœa were symptoms rather than essential and primary diseases." (V, i, 5, *see* also V, ii, 23.) "This was the course that was held by the fever throughout the autumn. Sometimes it attacked the head, sometimes the bowels. It everywhere put on the symptoms of the particular part affected. Such was the case till the end of October. At that time the weather, which had been as warm and as mild as summer, suddenly changed to wet and cold. This brought on coughs and catarrhs, which were more numerous than ever I remember them to have been. What, however, is of more importance, is the fact, that upon these coughs supervened the stationary fever of the year, and this, having once taken its hold, increased, and varied in some of its symptoms from the fever of the previous part of the year. The attack of the previous fever had been chiefly determined towards the head and bowels, that of the present towards the lungs and pleura, and as such gave rise to the symptoms of pneumonia and pleurisy."

(V, i, 6.) . . . Like the diarrhœa and dysentery before them they were both symptoms. . . The fever "was neither more nor less than what it had been throughout." . . . Its character being " that of the family into which it is adopted." (V, v, 1-3.) . . . "The catarrhs and coughs continued until the end of November, and then suddenly decreased. The fever, however, remained as before, just as it was before the catarrhs." (V, i, 7.) " All that suffered, suffered first in the head, back and limbs ; these being the symptoms, which were most constant to the non-pleuritic fevers which preceded, and which characterised them to their close." (VI, i, 6.)

In fact, by a reversal, so to speak, of the process by which it had emerged (V, i, 5), from the comatose fevers of 1673, 1674, and of the early part of 1675 and, indeed, from still earlier fevers (V, ii, 18), the stationary fever now became transformed into the comatose fever of 1675-6 (V, i, 7) and as will shortly be seen into subsequent fevers.

(*b*) *Transition from the fevers near the crests of the waves to those a little removed therefrom.* The next Constitution (1678-80) was that of Intermittents, of which we have two separate accounts by Sydenham and one by Willis. Willis had described cerebral complications in 1661, and Sydenham had then alluded to " mania " (M.O., I, v, 53) to "frenzies" (M.O., I, iv, 7) and to the " crude matter falling upon the brain " (M.O., I, iv, 25). He insists that the " fever which ran parallel with the intermittents easily became converted into an intermittent " (M.O., V, vi, 2) ; the said

fever was one in which "Nature has so modified all the symptoms as to dispose the febrile matter by a proper preparation through a regular coction for its proper outlet. . . . For this reason I call it the depuratory fever. Indeed, I am easily brought to believe that this is the principal and standard fever of Nature . . . of all fevers the commonest in respect to its occurrence." (V, vi, 1.) He thus looks upon it apparently as we do nowadays upon "endemic influenza," as a kind of thread (sometimes, truly, an almost invisible one) upon which are strung like beads successive prevalences popularly described as "new diseases" (to quote the sixteenth or seventeenth century phrase)—or, alternatively, as "popular diseases" (in the language of Willis and Freind) —while the term "new disease" again reappears in the eighteenth and early nineteenth centuries, but in the later nineteenth century Jenner's three continued fevers become paramount, and it is not until quite recent years that so-called "new diseases" again emerge to view.

(*c*) *Interchangeability of the fevers of the troughs.* At first Sydenham thought there was only one continued fever, then came the pestilential fever and, as years went by, others followed to which distinctive names as already noted were given. In V, vi, 6 he discusses some points of difference between the fevers of his earlier Constitutions. But already in 1676 (V, v, 1-3, and V, vi, 1-2) he seems to have realised that the stationary fever of his first Constitution bore close resemblance to that later stationary fever of the winter of 1675, viz., to the "depuratory fever," the "standard fever of Nature" . . .

" the fever to which Hippocrates dedicated his admirable and necessary axioms," and " upon which the other great physicians of antiquity have commented " (*see* also 58b. Letter to Dr. Brady, paras 54-57).

Moreover, it must never be forgotten that in certain Constitutions, those in which the continued fevers " ran parallel with the intermittents," the continued and intermittent fevers might prove to be indistinguishable from one another. (See above.) In the letter just cited (para. 56), Sydenham observes, however, that, in Intermittents, " Nature works hastily, and gets over in less time than is regular the processes whereby she first tempers and afterwards discharges the morbific matter. Depuratory fevers are different. Thirteen or fourteen days elapse before the appearance of any signs of the concoction of the febrile matter, which is then to be ejected by sweats, or rather by a somewhat free transpiration." And, again (para. 57), he describes how an earlier constitution " changed or laid aside its violence, lost its strength, and produced only humoral or earthy fevers—fevers which cleared the blood but slowly—whilst the fevers which were earlier in date, subtle in principle, and intermittent in type, did their work more rapidly."

(*d*) *Transition from the fevers of the troughs to those preceding the next great influenza.* The changes here may be studied in detail in the descriptions given by Sydenham of his Constitutions VII, VIII and IX.

The first two are described in the letter to Dr. Brady, the original of which carries us up to 1680, but in the revised second edition (dated 1685) paragraphs 56-59

are inserted: then there is a postscript added to the Tractate on Dropsy in 1685, and, finally, a full account is given of Constitution IX, that of 1685-6, in Schedula Monitoria I. In each of these writings illuminating sidelights are cast on the descriptions appearing elsewhere. In the Brady letter (para. 57) we find Sydenham expressing the fear that, as the outcome of the fevers of 1678-80, there would follow a "depuratory fever," like that of 1661-4; and that this might possibly be succeeded by plague. Happily this did not prove to be the case. The epidemic coughs which prevailed in 1679 greatly interested Sydenham, and after much cogitation he wrote his Postscript to the Tractate on Dropsy to correct his first impression that the cough was something quite new; he expressed the opinion that it was just an "intercurrent" and should be called the "winter fever"; then later (Sched. Mon. I, 4) he explains that, while at first disposed to regard this "winter fever" as an "intercurrent," i.e., a "bastard peripneumony which occurs in all winters alike," he now realises that it was the fever of a new constitution, and he describes it accordingly, in full detail (Sched. Mon. I). In his final paragraph (l.c. 46) he again says of this new fever, "It may be a spirituous and subtle beginning of something else—the germ, perhaps, of the depuratory fever, now exploded, but which the plague followed." He gives reasons for this belief, but, as everyone may now know, it was influenza (the influenza of 1688) and not plague, that proved to be the "something else."

These three successive writings of Sydenham are

exceedingly interesting, as they help us to trace the gradual development of the view, which he at length well-nigh accepted, that depuratory fever, winter fever, the " new fever " beginning in February and lasting through the summer of 1685 (Sch. Mon. I, 4), and the " something else " of which it was a " spirituous and subtle beginning," all formed successive elements in what would now be called a " moving continuity." In the light of modern knowledge of influenza we cannot surely fail to recognise the real nature of all these prevalences.

The changes of type presented in the successive prevalences of 1675-88 have thus been traced, and we clearly discern (following upon the influenza of 1675) transitions from " fevers subtle in principle and intermittent in type, which did their work more rapidly," to " humoral and earthy fevers, which cleared the blood but slowly " ; then in due course there is a return to the subtle, intermittent type, which ushers in the influenza of 1688.

Such a sequence of events fits in with the view now held that the virus of influenza works more easily and rapidly near the crests of the pandemics, and with more difficulty and more slowly in the intervening troughs. Study of the London measles wave had already made it clear that successive accumulations of susceptible children, practically speaking, determine the comparatively simple form of the epidemic wave in that disease. The measles germ is, however, uniquely stable, and the incubation period of measles is fairly constant. In the much more complex influenza (it was urged) it becomes necessary

to recognise marked *variability*, the average time required for spread of infection tending to increase, in passing from the crest to the trough, and then again to diminish between the trough and next succeeding crest of each great pandemic wave. Moreover, in in fluenza (in contrast with measles) there are huge ocean rollers whose crests correspond to the pandemics, while, on the slopes and in the troughs of these great waves there are superimposed minor oscillations. The wave lengths of these minor waves increase, from less than a year to some five, or even seven years, proceeding from crest to trough, and correspondingly decrease again from trough to crest of the great waves.

As to the significance of these transitions from one stationary fever to another, there can be no doubt remaining after putting together the evidence forthcoming in recent years and that of the cycles of Sydenham's time; and the reasons for assuming that these transitions are associated with lengthening of the incubation period of influenza (from something like a few hours on the crest, to a week or ten days in the trough of a great wave of influenza) have been referred to elsewhere (25p, 60-61); certain considerations in support of the thesis as a whole may, however, be mentioned here.

In the *first* place, we are now learning to recognise "endemic influenza," or, as it has been termed, "influenza in mufti." Given *that*, Sydenham's transitions become much more understandable. We begin to realise, moreover, the true meaning of Hirsch's dictum (29) that "Few among the acute infective diseases have manifested

in their prevalence at all times and in all places, the stamp of uniformity so strongly *in the aggregate of symptoms* as influenza. It is yet once again a case of "plus ça change plus c'est la même chose." Such a thesis of course entails abandonment of the belief that cerebro-spinal fever, poliomyelitis, and encephalitis lethargica are "new diseases." We here follow Sydenham who, when he came across a "new disease" felt impelled to try to give it a place in that "whole cycle of epidemics" of which he speaks (M.O., I, ii, 23). We must further regard with grave suspicion the doctrine that sweating sickness, typhus and relapsing fever are extinct; the first-named reappeared in France in the eighteenth and nineteenth centuries and the last two again emerged to view on the great scale, during the last twelve years, in Serbia, Russia and Poland, where they seem to have taken the place of those epidemic diseases of the central nervous system, which have been so much in evidence in other countries.

Then, *second*, we have to remember that the occurrence of annual, or biennial waves of influenza, intermediately between the crests and the troughs of the great interpandemic waves, may be favoured by the seasonal influences to which influenza is so susceptible; just as, in the troughs themselves, development of longer or shorter multiannual waves may be associated with special environmental conditions. The existence of great waves of "fevers" (upon the crests of which appear the pandemic influenzas), with lesser waves of "fevers" (surmounted by minor prevalences of influenza) intervening

between them, is strikingly illustrated by study of the figures, given in the Bills of Mortality of the eighteenth and early nineteenth centuries, and of those of later registration times (see pp. 138 and 140).

Then *third*, there has presumably been an evolution of the influenzal constitution itself, discernible when the history of the last five hundred years is passed in review. Thus, endemic influenza may tend to present somewhat differing characters now, from those of the "depuratory fever" of Sydenham's day. In this connection, however, a consideration, which must not be ignored, is that emphasised by Sir William Jenner, who remarks (32, 2) upon the graver signs of typhus, and particularly the petechiæ, as being apt to be encountered in an unfavourable environment. Thus the famine and overcrowding of the "hungry forties" (in England and particularly in Ireland); of the British and French troops in the Crimea in "the fifties"; and of the Lancashire population in the cotton famine, resulting from the American Civil War; these all helped to bring a "typhus type" of fever to the fore in the middle third of the nineteenth century; and similar conditions undoubtedly operated in Eastern Europe in the Great War.

Finally, there is the similarity of the proportion borne by "fevers" to "all causes" of death, in Sydenham's time and in our own. A correspondence, such as might have been anticipated, is discernible here, provided the greatly increased facilities for infection, resulting from the immense growth of intercommunication and traffic (on the one hand) are balanced against improved hospital

and nursing treatment (on the other). This fact points to a marked degree of continuity and persistency in the influenzal group of diseases.

Considerations, such as those outlined above, clearly justify the claim that there is a very close family resemblance between certain " Constitutions " described by Sydenham and the " Settings " of the Ministry of Health Report of 1920. The premises, upon which conclusions may now be based, are vastly more extensive than two hundred and fifty years ago, but study of Sydenham suggests that the Epidemiology worked out by him is broadly speaking applicable to the phenomena forthcoming in the twentieth century. In his description of the Constitution of 1673-76, he undoubtedly gives the clue to the problem of the " setting " of subsequent influenzas ; again, he realised that his next succeeding constitution (1678-80) was a replica of that of 1661-4 and he seems to have thought of it as starting a new cycle, and to have held that there would be more of them in years to come ; perhaps the most curious fact of all is that he recognised that his " depuratory fever," with its crisis on the thirteenth or fourteenth day was transformable, into and from, fevers in which " Nature works hastily and gets over (processes) in less time than is regular." We cannot but marvel at his insight, but must at the same time wonder whether such discernment may not have been facilitated by the fact that the complexity of constitutions was rather less marked in the middle of the seventeenth century, than it is now. And yet how close the resemblances are. The change from the (possibly) more

homogeneous of the seventeenth, to the (possibly) more heterogeneous of the twentieth century, is surely no greater than might have been anticipated from an evolutionary point of view.

It has been argued (25p, p. 74) that the menace of influenza (as judged by death-rates) in the London of to-day, is less than it was near the middle of the eighteenth century, at which time it appears to have reached its culminating point. If this be true, it is a strange comment, on the Greek opinion—dating from Aristotle's time and unearthed by Creighton (Traill, 60, p. 508), from its concealment in an Appendix to Stow's Survey of London—to the effect that "ten thousand persons was the largest community that could be well governed, fed and kept in health."

CHAPTER III

THE HISTORY OF EPIDEMIOLOGY DURING THE LAST HUNDRED YEARS

(i) The Germ Theory and the Old Epidemiology

On a cursory view, the history of Epidemiology brings to mind Swift's account of the controversies of the Lilliputians. During his first nine months' residence in Lilliput, Gulliver became greatly interested in some of these animated disputes, which were "significant of much"; that of the Tramecksan and Slamecksan, who for seventy moons past had been distinguished from each other by the high and low heels of their shoes, and that of the Little Endians and Big Endians, who disputed as to the proper way of breaking eggs. With regard to the latter, Gulliver, who appears to have acquired an intimate acquaintance with the language of Lilliput in a remarkably short time, and to have read many hundreds of books on the question at issue, concluded that the differences concerning breaking eggs were merely of a textual character, for, says he, going back to the origin of the whole dispute, the authoritative words are these: "All true believers break their eggs at the convenient end." This is an unexpected volte face, coming as it

does from a man who had been apprenticed for four years to a medical practitioner, had studied medicine at a Dutch University and had had experience as a ship's surgeon; if he had but completed his training by studying Epidemiology he would doubtless have been disposed to favour the Big Endian point of view.

In March, 1918, on the appearance of a new disease, controversy raged in London as to whether food poisoning or encephalitis was in question; on the one hand, likenesses and affinities with recognised types of diseases; on the other, differences were stressed. The episode tended to emphasise the correctness of Sydenham's view that "the brief life of a single mortal" is not long enough to demonstrate "the fact of certain epidemics succeeding each other regularly and in series forming as it were a circle." He, however, when he was confronted with somewhat similar phenomena, in his "epidemic constitution" of 1673-76, the counterpart of our pandemic prevalences round about 1918, was moved to say "All that I know is what I know well; namely that up to the present time it has been exceedingly anomalous and irregular, and that all the diseases which have originated from it have been the same" (M.O., V, i, 7).

This difference of outlook, in Sydenham's time as compared with to-day, makes us recognise that in epidemiology, as in all branches of scientific enquiry, "General Climates of Opinion" are successively encountered. Professor Whitehead (64b), who borrows this phrase from an author of Sydenham's century, goes on to explain that such "Climates" persist about two or

three generations, that is to say for periods of sixty to one hundred years; in his "Science and the Modern World" he gives account of four such periods immediately preceding our present Climate (see p. 109). They are, first, the "Century of Genius" from Galileo, Kepler and Shakspere, to Harvey, Milton, Sydenham and Newton; next comes the eighteenth century, termed by Carlyle (whom Prof. Whitehead quotes) the "Century of Victorious Analysis"—the age of the great French mathematicians and of Kant, Lamarck, Watt and Volta; then follows an interlude, Prof. Whitehead terms it the "Romantic Age," with Wordsworth, Shelley, Keats, Schubert, Carlyle and Faraday; next in order there appears the "Age of Professionalism," practically coincident with the nineteenth century, but tending to peter out towards its termination, so that "in its last twenty years the century closed," says Prof. Whitehead, with "one of the dullest stages of thought since the time of the First Crusade." (64b, 6.) It was an interlude of "decadence," "decline," say some; Miss Rose Macaulay prefers to call it a period heralding in advance; upon it followed the modern era, with its revival of the doctrine of Relativity. Prof. Whitehead says, "The new tinge to modern minds is a vehement and passionate interest in the relation of general principles to irreducible and stubborn facts. All the world over and at all times there have been practical men absorbed in irreducible and stubborn facts; all the world over and at all times there have been men of philosophical temperament, who have been absorbed in

the weaving of general principles. It is this union, of passionate interest in the detailed facts with equal devotion to abstract generalisation, which forms the novelty in our present society. Previously it had appeared sporadically and as if by chance. This balance of mind has now become part of the tradition which infects cultivated thought."

Dr. Brownlee's view may be compared and contrasted with that of Prof. Whitehead. In 1908 Dr. Brownlee (4b) read a paper before the Royal Philosophical Society of Glasgow, entitled "Germinal Vitality; a study of the Growth of Nations as an instance of a hitherto undescribed Factor in Evolution." In this paper special stress was laid on germinal activity and growth of population as a whole, while, incidentally, Dr. Brownlee made some very interesting observations on periodicity in the manifestation of genius. He states that "Each period of English energy since the Conquest is associated with increase of population, and if this held also for the period of the Saxon invasion, then up till the present time there have been five waves of expansion, with four intervening periods, in which there was no national response to the intellectual action of the few great men who lived or ruled during these times of depresssion." Dr. Brownlee's five waves cover 450-550 A.D., 650-800, 1290-1390 (the age of Dante and Chaucer), then the age from Shakspere to Milton (Prof. Whitehead's Century of Genius), and finally a period which "runs from 1760-1870," thus covering Prof. Whitehead's next three epochs and bringing us to the dawn of his new mentality.

Dr. Brownlee pointed out that his periods do not absolutely coincide in different countries. Thus Spain doubled its population in the sixteenth century and, thereafter " began to occupy a less prominent place." France stood well before the Black Death, and then again in the reign of Louis XI ; by 1550 its population had reached " the numbers previously attained before the plague " ; then came a period of " weak germinal energy," followed by " strong germinal energy " in the days of Richelieu and Louis XIV. After 1685 there was again retrocession, and then once more increase, from the Revolution until about 1830-40. As regards our own country, Dr. Brownlee said : " Three times in history the population has doubled itself within a hundred years. (Once in the hundred years preceding the Black Death and again in the sixteenth century and between 1760 and 1860.) The Renaissance is said not to have reached England for a full century after it had pervaded the Continent," but this simply means, Dr. Brownlee said, " that the Renaissance found England in a stage of physical inertness, but the moment the physical condition of the race became attuned to the new thought, that moment it found expression in England."

Again, he said, " The effect of pestilences and famines must clearly be looked for in relation to the physical state of a people. Thus the Black Death, in 1348, little lessened the energies of England ; Poictiers was fought in 1356, and the response of the people to the sovereign's policy was that of an energetic nation." On the other hand, " The plague in Athens was the mark of the end of

a period. The population had passed their period of increase, and recuperation was necessarily a slow and uncertain process. The decline of Athens was not so much due to the loss of actual numbers of those destroyed by the disease, as to the fact that already at the time of the plague, the supply of capable individuals, who in general form the backbone of a governing people, had become deficient, for there is no reason to suppose that these were specially killed off by the disease."

Sir Ronald Ross (51) in his work on Malaria refers to enquiries made on the influence of malaria in promoting the decline of the Greek civilisation; and this suggests that, in these later centuries, the influence upon civilisation, germinal vitality, genius production and the like, of influenza, is deserving of study. This notion has been especially borne in upon the minds of observers of the great epidemics of influenza, in the "nineties" and in the years 1915-27. Sir George Savage (53) was wont to lay stress on the effect produced upon the nervous system by the former; and recent studies of the relation between influenza and those epidemic diseases of the nervous system, which are apt to accompany (or rather shortly to precede and follow upon) the great universal influenzas, has again aroused interest in this problem.

A year or two ago the dates of birth of the men of genius, whose names appear in Frederick Harrison's *New Calendar of Great Men* were plotted out; and then, later (as regards 250 of those best known in the Calendar), there were marked on ruled paper, from 1550 onwards, the years corresponding to three successive sections of

the lives of these men. By counting up the number of intersections of the life lines thus indicated with the vertical lines on the ruled paper (representing single years),

Waves constructed from data taken from the "new Calendar of Great Men."	Prof. Whitehead's Climates of Opinion.	Brownlee's two latest Waves of Germinal Influence.
1550 to 1705 — Cervantes, Tycho Brahe, Shakspere, Kepler, Bacon, Galileo, Harvey, Milton, Velasquez, Sydenham, Descartes, Pascal, Spinoza, Molière, Locke, Boyle, Newton, Leibnitz.	"*Century of Genius.*"	The antepenultimate wave of Brownlee extending as it does from Shakspere to Milton practically coincides with the two preceding columns.
Morgagni, Bach, Berkeley and Jonathan Swift lived their lives in the trough between these two waves, 1680-1720.		Dr. B. describes a "Critical Age" corresponding with this trough.
1705 to 1805 — Kant, Euler, Lagrange, Watt, Lavoisier, Laplace, Priestley, Dalton, Lamarck, Beethoven, Fourier, Hegel, Goethe, Wordsworth, Coleridge, Byron, Scott, Shelley, Keats, J. Austen, Schubert, Faraday, Carlyle	"*Century of Victorious Analysis.*" / "Romantic Reaction."	Dr. Brownlee's final wave extended from 1760 to 1870.
Carlyle, Byron and Faraday lived some years between these waves.		
1805 to 1885 — Dickens, Tennyson, Browning, Schumann, Chopin, Mill, Graham, Chadwick, Farr, Darwin, Huxley, Tyndall, Pasteur, Canizzaro, Mendel, Maxwell, Helmholtz, Virchow, Kelvin, Kekulé.	"*Century of Professionalism.*"	
S. L. Clemens, W. James, Hertz, Röntgen, Koch, and Creighton lived through this trough.		
1905 onwards. Thomson, Van't Hoff, Arrhenius, Edison, Rutherford, Lorentz, Einstein, Marconi.		

it was possible to construct the graphs, whose ordinates represented the numbers of intersections at 0-25, 25-30, and 50-75 years of age. These three graphs were, of

course, very nearly the same in form, each being, however, twenty-five years behind its predecessor. The object originally held in view was to compare these graphs with the periods of rise and fall of the great waves of influenza. The graphs (p. 152) clearly present three successive waves, corresponding with the "Climates of Opinion" and the "Germinal activity periods" to which reference has been made, and which the preceding Table also shows.

Mr. Havelock Ellis's *A Study of British Genius* based on an analysis of the characteristics of 1,030 persons whose names appear in the Dictionary of National Biography confirms, so far as it goes, the general scheme set out in the above Table.

What special influences, epidemiologically considered, have "climates of opinion" exhibited? Dr. Crookshank (10a, 3), as already noted, has stated, in discussing "epidemic encephalomyelitis" that "In the last 450 years four periods seem to be indicated; four periods marked by different phases of medical thought and observation. The first (he says) closes with the era of Willis and Sydenham," i.e., covers Prof. Whitehead's Century of Genius (commencing, however, just a little before it); in it "wide epidemic prevalences were observed and compared, as a rule, without resolution into component diseases, and symptoms obviously due to forms of meningitis, encephalitis and myelitis, were described in relation to occurrences that we would now call disease groups." Thus, in medicine, too, this period was one of genius, it was the age of Harvey and Sydenham,

and thus saw both the inauguration of the experimental and the revival of the natural history methods of studying disease. It will be found in the next chapter that there is a notable revival of interest, nowadays, in this period. The second period of Dr. Crookshank, like that of Prof. Whitehead, covers the eighteenth century ; this, the age of " Victorious Analysis," is described by Crookshank from his standpoint, as an age when systems of nosology were based upon symptoms, the symptom groups in question being "usually considered as different elements of special epidemic constitutions" ; it was a period of great growth, of population and material resources, in Europe, with commencement of even more rapid growth in N. America ; it witnessed, moreover, the French Revolution and the inauguration of the Industrial Revolution. Incidentally, it may be noted that the developments at this time in inter-communication and traffic had considerable influence in favouring the spread of epidemic diseases ; nevertheless during the century plague disappeared from Europe and towards its close considerable improvements in the public health and in social services were effected.

Crookshank's next period (corresponding with Prof. Whitehead's " Age of Professionalism ") began in 1800, and in it, appropriately enough, " Persistent efforts were made to distinguish specific diseases by the findings of morbid anatomy." Population and means of communication in Europe and America grew by leaps and bounds. Cholera spread from Asia into Europe and caused much mortality ; and influenza was phenomenally

rife in the middle third of the century. Influenza again became pandemic in the " nineties."

Crookshank's fourth period, beginning some forty years ago, " is characterised by the distinction of many specific diseases by association with specific organisms." In this connection it is interesting to recall the remarks by Dr. Goodall (21a, p. 119), already quoted on p. 13. Prof. Whitehead presumably had not these characterisations in mind when he affirmed that the commencement of the said fourth period was comparable, intellectually speaking, with the time of the First Crusade (64b, p. 143). He, however, evidently considers that release at length came from an environment, which might almost be described as one of captivity and bondage, in the early years of the present century. The new century has already had a great influenzal constitution of its own, that of 1915-25.

Did time permit, further light could be thrown on the study of epidemiological affinities in the period covered, from four hundred and fifty to one hundred years ago, by quoting illustrative passages from the essays in Crookshank's *Influenza: Essays by several Authors* (10a); in particular, his reference to Fernel, p. 39, with the proof it affords that already, in Picardy, in the fifteenth century, epidemic catarrhs were associated with faucial, tracheal, pulmonary and nervous complications (including paralysis, stupor and tremors and disorders of the special senses), is of great interest for epidemiologists—a voice crying in the wilderness more than four hundred years ago; again, Crookshank cites Boström of Upsala (p. 44), as a witness some three centuries later (1756-58), to corresponding

occurrences of nervous, pulmonary and gastro-intestinal prevalences in association with catarrhal, nervous and contagious petechial fevers; furthermore, Crookshank points out that half a century later Zeviani (p. 46) (1800-03) testified to the association of influenza with "malignant nervous fever, peripneumonia and a phthisis." In a later chapter, Dr. Crookshank makes comparison between our encephalitis lethargica of 1918 and the paraplegia of Thasos, described by Hippocrates more than two thousand years ago (p. 82), and he also refers to the "avant coureur" of influenza commented on by Ballonius in 1576, and to the outbreak at Lüneburg in 1581, to the "mal mazzuco" of 1597 (pp. 86 and 87) and to the epidemic lethargy (coincident with Willis's prevalences of 1657-8) noted by Bartholin at Copenhagen (p. 88), and finally to that unmistakable encephalitis lethargica, the "Schlafkrankheit" described by R. J. Kammermeister (Camerarius) at Tübingen in 1712, to that still more vividly depicted by Guidetti of Turin in the same year, and to the later "encephalitis myoclonica" of Elias Camerarius in 1729.

These particulars are here merely alluded to, as indicating the quality of the lodes of rich ore hidden away in the epidemiological literature, and now laid bare by Dr. Crookshank's untiring industry for exploitation by epidemiologists; and more especially for the reason that they exemplify the contrasts between the two points of view, that of the older epidemiologists, and that of decades with an intellectual outlook comparable with that of the First Crusade.

It was necessary, as a preliminary step, to sketch in broad outline the influences exerted by epidemic diseases upon the progress of civilisation, before approaching the special subject under present consideration. We have now reached the downward slope of Prof. Whitehead's third wave, and have to deal with the Age of Professionalism and with the immediate aftermath thereof. The period we are concerned with begins upon a rising wave of genius and on the flood of the "New Momenta," of which Sir John Simon speaks in his English Sanitary Institutions; death-rates are falling, population and industry rapidly growing, but cholera is rife on the Continent.

So far as epidemiology is concerned, the atmosphere at the commencement of the nineteenth century might be described in almost as gloomy terms as those Prof. Whitehead applies to the decade at the century's close. J. F. C. Hecker, in an address, nearly a hundred years ago, to the Physicians of Germany, asks what are we medical men of to-day doing, as regards investigating epidemic disease, "on a scale commensurate with the extent of our exertions in other departments and worthy of the age in which we live." . . . "Are we," he says, "trying to penetrate with becoming reverence into the sanctuary of cosmical and microcosmical science. . . . Has medical science, as it exists in our days, with all the splendour which surrounds it" (Germany, it must be remembered, had already taken the lead in the patient and indefatigable work of the then commencing Century of Professionalism), "with all the perfection of which it boasts, satisfied this demand? This

question we are obliged to answer in the negative." He describes how the doctrine of diseases "nurtured by the storms of centuries" . . . now "speaks clearly to the initiated in the languages of all civilised nations. Yet hitherto it has given an account only of individual diseases, so far as the human mind can discern their nature. In this it has succeeded admirably, and its success becomes every year greater and more extensive. But if we extend our enquiries to the diseases of nations, and of the whole human race, science is mute . . . shows us only an immeasurable and unexplored country, which many suppose to be merely a barren desert. . . . Small is the number of those who have traversed it, often have they arrested their steps, filled with admiration at striking phenomena; have beheld inexhaustible mines waiting only for the hand of the labourer, and, from contemplating the development of collective animal life, which science nowhere else displays to them on so magnificent a scale, have experienced all the sacred joy of the naturalist, to whom a higher source of knowledge has been opened. Yet could they not make themselves heard in the noisy tumult of the markets, and still less answer the innumerable questions directed to them by many as from one mouth, not indeed to inquire after the truth, but to obtain a confirmation of an anciently received opinion, which originated in the fifth century before our era."

Hecker's appeal in Germany is an indication of the new spirit that was stirring in this country; and one of the first results, here, was the passing of the Public Health

Act of 1848, establishing a General Board of Health, which was to continue in operation "for five years and to the end of the then next session of Parliament." The achievements of this Board will always be associated very specially with the memory of three men. Simon relates how "the crucial work of the Board's first six years was carried out, apart from the four successive *ex-officio* members, by Edwin Chadwick, by an unpaid member Lord Ashley (who in 1851 became Earl of Shaftesbury), and (after its first two years of existence) by a medical member, Dr. Southwood Smith." In his account of the struggle between the board and the "interests" opposed to its policy, Simon says that "most of the force of the attack was aimed personally at Mr. Chadwick" and it was he who bore "the distinction, which has been many a great reformer's crown of laurel, that he was among the best abused men of his time." Simon counts among the causes of the resistance encountered, which wrecked the first Board in 1854, partly that the time was one of standstill, intervening between times of progress, partly that as Lord John Russell said, "Obviously many towns would rather be let alone . . . there were likewise many persons who were pecuniarily interested that the plans of the Board should not be adopted, and it was very probable that Mr. Chadwick had not observed towards these classes of persons the most conciliatory tone possible." Upon this Simon points out "That patience under sufferings of one's own and patience towards the sufferings of others are not equal measures of magnanimity. Mr. Chadwick, beyond any man of

his time, knew what large fresh additions of human misery were accruing day by day, under the then almost universal prevalence of sanitary neglect; and the indignation which he was entitled to feel at the spectacle of so much needless human suffering is a not ignoble excuse for such signs of over-eagerness as he may have shown." To the ten years' hard work of Mr. Chadwick prior to 1848 "The nation unquestionably owes," says Simon, "that our statesmen of those times were first awakened to the duty of caring for the Public Health, and that the first of our modern legislative endeavours were made to bring Health under the protection of Law."

While the humanitarian spirit had then thus at length begun to find practical expression, the thirst for scientific enquiry concerning the laws of hygiene was also aroused. The stirring appeal of Hecker had evoked a fine response in Germany, and Dr. Babington, the translator of Hecker, found himself, in 1850, the first President of the Epidemiological Society of London, a Society to which tribute was paid some thirty years later by Dr. Hirsch, in the Preface to the translation of his great work by Dr. Charles Creighton. Moreover, a certain Dr. Farr was appointed in 1839 as Compiler of Abstracts in the Registrar-General's Office, "An appointment," says Simon, "which seems to have been due to Mr. Chadwick's early recognition of his merits." Medicine was thus addressing itself to the task of penetrating into the sanctuary of "cosmical as well as of micro-cosmical" science.

But the foundations of the new epidemiology in this country were once and for all well and truly laid by the men who suffered shipwreck in the crisis of 1854. "The 'interests' which had clamoured against them had every reason to be satisfied, but," says Simon, "the world around them was an 'interest' which had raised no voice. The nation which was so much in need of proper sanitary government, the millions of population still under the free ravages of preventable disease, had not yet the self-consciousness of an interest." It was the first awakening of it that, "even in the moment of wreck," secured the continuance of a newly constituted Board of Health until 1858—to be followed by a Medical Department under the Privy Council (passing some years later under the Local Government Board, then newly constituted by the Act of 1871), a Department which also earned encomiums from Prof. Hirsch in 1883, and was destined to develop ten years ago into the Medical Department of the Ministry of Health. It was the interest, thus increasingly manifested by the millions of population, who had once been "under the free ravages of preventable disease," which gave new life to epidemiology, and did so much for the welfare of that still very youthful science.

Hecker, in his address to the physicians of Germany, had lamented that epidemiology did not make itself "heard in the noisy tumult of the markets,' and he added "Hence it is that the doctrine of epidemics, surrounded by the other flourishing branches of medicine, remains alone unfruitful, we might almost say stunted in its growth. For to the weighty opinions of Hippocrates,

to the doctrines of Fracastoro, which contain the experience of the much tried Middle Ages, and lastly to the observations of Sydenham, only trifling and isolated facts have been added."

The frontal attack had, however, been delivered upon "filth diseases," "houses unfit for habitation" and the "free ravages of preventable disease," and one of the early results of this assault was the realisation of the fact that, as Hirsch put it, in 1883, in his Preface already referred to, there were also needed "the founding according to a design, and the building up according to a system, of a discipline which had been the subject of but little labour before, and had still to make good its right to a place among the Medical Sciences." He was able, however, to say (at that date) "Epidemiology bears a character quite different from that of the science twenty or thirty years ago. It has filled out in proportions and acquired finish to an extraordinary degree."

In illustration of the "finish" referred to, note may be made of an essay by Hecker himself on the "English Sweat" (27b), profoundly interesting on account of the light it throws on our modern influenza. A diagram, which appeared in the Milroy Lectures of 1906, sets out the main facts recorded in the Chronological Survey first published by Hecker in 1834. It shows how in the fifteenth and sixteenth centuries, the countries of Europe were contemporaneously devastated by widespread prevalences of epidemic disease. The first English Sweat was immediately preceded by "hauptkrankheit" in Westphalia, Hesse and Friesland, "epidemic pleuritis"

in Italy and " febrile cerebritis " in France, and developed coincidently with " malignant fever " in Germany and " plague " in Spain . . . diseases " which in their widespread prevalence, involving whole nations, and sudden devastating character, it is hard to match " save with prevalences such as those of the " nineties " and of 1915-25. " Just prior to the second sweat there appeared similar outbreaks in France and Germany, and also in Spain and Portugal—in Spain they continued until they culminated in the Influenza of 1510." It thus appears that, coincidently with the " Influenza " of 1510 in Britain, " sweating sickness " prevailed in Spain. " The third English Sweat admittedly invaded Calais and contemporaneously there was ' hauptkrankheit ' (as before) in Germany and a mysterious epidemic disease in Holland " . . . " lasting only eleven days," presumably an influenza. The fourth sweat, again, was not peculiarly English, but " it spared France "; that country, however, had a " trousse galant " of its own, doubtless influenza under another name. At this time it is on record that Cork, in Ireland, suffered from " the sweat." Again in Hecker's words, "the fifth epidemic Sweating Sickness appeared, accompanied by a group of various epidemic diseases, which might be considered as resulting from general influences " ? But, what was this " group of various epidemic diseases " ? Brassavola, writing almost contemporaneously, speaks of a sweat that vexed Flanders, in 1551, this year of the fifth English Sweat at home. And, as Crookshank (10e) has shown, in a closely reasoned discussion of the Trousse-galants of

1528-9 and 1545-6, this sweat in Flanders was contemporaneous with a *coqueluche*—surely influenzal—in Paris, with epidemic pneumonia and fevers in Germany and Switzerland, with obvious influenza in Swabia, with fever and encephalitis in Italy, and with epidemic encephalitis in Siberia. May it not then be said that the "arguable proposition" of a friendly but rather sceptical critic of nine years ago (*Brit. Med. Jour.*, 1919, ii, 386) has been fairly translated into "an undoubted fact"?

In the light of the experiences of the "nineties" and of Creighton's reflections following thereon, it was already, in 1906, quite clear that "To cling to the individuality of the English Sweat and of similar forms of disease contemporaneously prevailing in the several Continental countries," was, epidemiologically considered, "an untenable position." To-day there are the additional experiences of 1915-25 to guide us, and it is possible to appreciate more fully, now, many of the telling touches in Hecker's description of the English Sweats, the interpretation of which was less obvious twenty years ago. Thus we are reminded, in reading about the English Sweat, not only of influenza, but also of the wide-spread prevalences occurring in association with it, described now as "encephalitis lethargica," now as "Japanese encephalomyelitis," or by yet other new—or in some parts of the world quite old and familiar—designations.

For example, Hecker mentions "lethargy" (pp. 191, 237, 277, 280, 304 and 363), "petechial fever and encephalitis" (p. 297), "hypochondriasis" (p. 259), "altered voice" (p. 308), "arms enfeebled," "palsies"

and "affections of the spinal marrow" (pp. 288, 245 and 280 respectively), "affections of the eighth pair of nerves" (i.e. of the vagi, pp. 191, 192, 282) and "fatal sopor" (pp. 268, 274, 281, 289, 309); the first and the last are, as now appears, particularly suggestive of the encephalitis of 1918.

Side by side with the references last mentioned may be placed those on pp. 277 and 304 to the remedial measures advocated by Damianus for restraining his patients from indulging their propensity to sleep, which were doubtless adapted from those used in the early English sweats; practices later mentioned with approval by Dr. Caius. Thus Damianus urged "When the usual means failed," that the patients' hair "should be torn out, that their limbs should be tied together in painful positions and that vinegar should be dropped into their eyes." These recurring insistencies of sixteenth century writers on the use of desperate measures in dealing with the most formidable symptom of the "English sweat," might at least "put wise" any diehard who may still hold that "encephalitis lethargica" is a new disease.

Furthermore, when we read Hecker's paragraphs on "Influenzas" (p. 218), his note (p. 222) on the sweating character of the influenza of 1580, and his remark (p. 223) that "he must at least point out the relation which the influenzas bear to the greater epidemics"; when (p. 200), we find him connecting "the petechial fever of Southern Europe with the sweating sickness of the North," and read his comments on the epidemics of 1517, especially noting (p. 227) that he feels "fully justified in

classifying those of Holland and Germany with the influenzas" ; and when finally he speaks of their " being a forerunner of the English pestilence, which was simultaneously prepared by the altered condition of the atmosphere and broke out a few months later," we must admit that he approached prodigiously close to identifying the English sweats with Influenza.

The prevision shown by Hecker may be matched by that later displayed by Creighton, the discoverer of the close association between influenzas and epidemic agues, when he placed in an Appendix to his great History of Epidemics in Britain (9d) a " Note on Cerebro-spinal Fever " ; in which, after commenting upon a case, occurring in March, 1894, in an eastern parish of London he added, " It is improbable that this was a solitary case of epidemic cerebro-spinal fever." As he said, " British experience, or the records of it (up to that time) afforded very little material for a history of epidemic cerebro-spinal fever (very abundant in France, Germany and the U.S.A.)" ; but he much doubted whether the " half dozen or so of deaths annually certified in London (as from that disease), contrasting with as many hundreds in New York, were of the slightest statistical value." Not many years later his anticipations were confirmed, for a notable prevalence of cerebro-spinal fever (1915) was developed in London, shortly preceding the great influenza of 1918, and the occurrence of such association, constituting part of the " setting " of pandemic influenza, has been now officially recognised.

A further illustration of the " finish," spoken of by

Hecker, is afforded by studies of Dengue, which have been made in tropical countries, and the outcome of these was shown in some maps which were prepared (in illustration of the Milroy Lectures of 1906), from material collected by the late Dr. Christie, supplemented by use of Hirsch's index to the literature of that disease. The maps demonstrate that widespread prevalences of Influenza and Dengue have throughout the epidemiological history tended to be interchangeable; each assuming the rôle which might have been allotted to the other. Thus the West Indian islands suffered from "influenza" in the world-wide prevalence of 1789-90, but in 1826-28 and in 1849-50, when influenza was again pandemic, "dengue" held the field in these islands; in subsequent years the West Indies reverted to use of the term "influenza." Similar phenomena can be traced in British India and in the East Indies.

But while epidemiological field work, on the Continent, in this country, in America and in the Tropics, was thus slowly building up an ordered system of records, a new development, potent no doubt ultimately for good, but attended temporarily by much counterbalancing retarding influence was now to be inaugurated. It is very interesting to recall the fact that as long ago as 1881, in a letter to the *Lancet*, Sir William Collins (7a) clearly pointed out that, while much had been achieved, there was already apparent a slackening in the rate of progress; he clearly saw, in fact, nearly half a century ago, the little cloud rising out of the ea no bigger than a man's hand, and prophesied the approaching storm. He

developed his thesis in an Abernethian Society paper in 1884, entitled "Specificity and Evolution in Disease," (7b), in which he said, "There can be no doubt that the tendency of pathology during the present century, thanks chiefly to the enormously increased means at our disposal for facilitating diagnosis, and fostered by the teaching of Bretonneau and Laennec, has been to specificise disease; and while the recognition of the doctrine of specificity has done much to push on our knowledge by insistence on detail, and the estimation of minute differences, it is quite possible that this tendency may have served its ends and surpassed its utility. That such is really the case we are frequently and forcibly reminded by disorders which come constantly before us, the so-called anomalous cases, where disease does not breed true, or where hybrid symptoms are developed, cases which do violence to our theories and defy our classification. It is easy enough to call such cases exceptional, to pass them by as abnormal and think we have so dismissed them, because they do not approximate to what we have been pleased to select as our types; but nature is uniform and not vagarious and will have none of these hard and fast definitions we seek to impose upon her." Sir William Collins added "the solution of this difficulty lies in a more thorough recognition of the doctrine of evolution as applied to disease, as ruling and directing specificity." He quotes Dr. Sansom and Sir Jas. Paget, who both insisted that "soil must be studied as well as seed," and illustrates his argument by detailed references to continued fevers, scarlet fever, diphtheria and other

diseases. Dr. J. T. C. Nash, in his Chadwick Lectures of 1913, and other followers of Sir William Collins, in more recent Chadwick Lectures, have made further contribution to this study of Evolution and Disease.

Meanwhile, the rain descended and the floods came and the winds blew and beat upon the epidemiological house. Pasteur's researches focussed attention upon germs, and Koch's special technique dates from the late "seventies" and the early "eighties." There were quite frequent announcements by those who were working at bacteriology in the "eighties" regarding the compliance of successive newly described organisms, with Koch's postulates. The old epidemiology, like the silk stockings of Sir John Cutler, was darned with worsted until so little of the original silk remained that no one could be sure that any of it was really left. The situation, it is true, became less strained when de Schweinitz, in 1903, demonstrated that hog-cholera was due to a "filter-passer," and not, as had been previously supposed, to the hog-cholera bacillus. Already, in 1894, Gottstein (23) had suggested that pathogenic germs might be merely playing the part of "associated organisms" (*jeweiligen Begleiter*) in established conditions of disease, and a few years later O. Liebreich put forward the conception of "Nosoparasites," i.e., of pathogenic germs which are not parasites proper, but parasites of diseases, that is "accompanying," or "secondary" organisms. Moreover, in 1908, Hottinger (30) declared that Koch's four conditions should be enlarged "by the addition of a requirement that the infectious character be exhibited by inoculated

animals," and speaking more generally, he adds, the condition should be insisted upon " that the artificially produced disease must fulfil the requirements of epidemiology."

In preparing, for the History of Medicine Section of the International Congress of Medicine, of 1913, a paper (25r) on " The History of Epidemiological Research during the last seventy years " (i.e., dating from the year 1843, when Pasteur came of age and Robert Koch was born) the influence of the great epidemics of the " thirties " and " forties," of Chadwick's strenuous labours, of the aspirations of German scholars and of the Epidemiological Society of London (founded in 1850) were all envisaged, and reference was made to Hirsch's dictum of 1881, that so great a change of outlook in Epidemiology had come about that what was now needed was " an entirely new treatment of the subject." It was also appreciated that bacteriology itself was beginning shortly after the end of the nineteenth century to recognise that a halt must be called for re-alignment. It was agreed that bacteriologists had then " outgrown Koch's postulates as Koch himself outgrew them," and that account must be taken of the results of fifty years' patient examination by epidemiologists " of the influence of environment, of conditions of filth, overcrowding, dampness, unwholesome and infected water, milk and food " ; all this, taken together with increasing knowledge of protozoology, filter passers, enzymes, and the recent demonstration of mutability of bacilli, made it clear that attention must still be concentrated upon the systematic

development of a discipline as conceived and exploited by Hirsch. It was accordingly urged that progress in knowledge of epidemic diseases was only to be gained by bringing about a "unity of opposites." As Prof. Caird says, "The thinker who has fully seen into the correlativity of given opposites has reached a new attitude of thought in regard to them. They have become to him inseparable elements of a higher unity, which is now seen to be organic or vital."

Thus while it was increasingly realised that the epidemiology of the Victorian era had laid too great stress upon the "symptom complex" and the "gross macroscopical lesion," and had acquiesced in the differentiation of epidemics from one another which should not be so differentiated, and while it was suggested "that recent study of the rôle played in disease by 'secondary invaders' possibly afforded part of the explanation of the diverging theories in these instances," it was also clear, on the other hand, that bacteriology had not been sufficiently careful in distinguishing causal from associated organisms. Moreover, just as Huxley, in the "fifties" declared that not even Herbert Spencer's diagnostic skill could drive him from an agnostic position with regard to transmutation of forms, and as this incredulity fell in face of the accumulating evidence, so Koch had imposed on the great majority of bacteriologists a like incredulity with regard to the acceptance of transmutation in the lowest known forms of life, and so too this incredulity was seen to stand in need of qualification. Lord Haldane had remarked, in 1913, how "Science

itself was being subjected to a criticism, which had cast a wholly new light upon it. . . . It was so in every department of human knowledge—the 'obstinate questionings' of Wordsworth had extended thereto. And in science they saw the negative brought up against the old doctrine, which caused a halt, but only until a larger point of view had been reached, in which the negative was incorporated."

Fifteen years ago, then, it was urged that more energy must be devoted to cultivation of Hirsch's discipline with the object of further filling out its proportions, and giving it more complete finish. But it was not at that time fully realised that a line of advance to be followed was already clearly marked out. The great influenzas of 1915 and onwards brought the rude awakening, stimulating epidemiological enquiry in much the same way as similar epidemics had done in times gone by. Now, however, the path had been blazed through the forest by a great epidemiologist, who already in 1894 had focussed attention upon the need for bringing into a higher unity the supposedly opposed teachings of Sydenham concerning Epidemic Constitutions, and of Pasteur and Koch regarding the germ theory of disease.

Dr. Creighton, who had rendered epidemiologists in these islands the signal service of translating for them Hirsch's great work (29) on Geographical and Historical Pathology, had published, in 1891, the first volume, and, in 1894, the second and final volume, of the *History of Epidemics in Britain*. Space does not permit of attempting to give an appreciation of those epoch-making

volumes; the most remarkable characteristic of the work is, that a pathologist by training, in an age when pathology (with the added prestige contributed by the new bacteriology) was steadily acquiring growing importance, calmly set to work to fill out the proportions and give more complete finish to the old Epidemiology. But this new teaching must form the theme of the next chapter.

CHAPTER IV

THE HISTORY OF EPIDEMIOLOGY DURING THE LAST HUNDRED YEARS

(ii) The Return to the Hippocratic Method

The sage Koheleth, "the Preacher" (14), who lived more than two thousand years ago, said there was "no new thing under the sun." The thought is that of the "Persistence in Change" (*Dauer im Wechsel*) of Goethe, who elsewhere says "Everything that is wise has been thought already; we can only try to think it once more." Some have surmised that Koheleth was a physician, and certain passages in the Book of Ecclesiastes support this view, and may almost be said to anticipate the first Aphorism of Hippocrates, or even Sydenham's doctrine that "Epidemics succeed each other regularly and in series forming as it were a circle." A verse much commented upon runs: "He hath made every thing beautiful in his time: also he hath set the world in their heart, so that no man can find out the work that God maketh from the beginning to the end." It is said, that the word translated "world" should be rendered "eternity" (or "history"), and such renderings prompt the suggestion that Koheleth was a bit of an epidemiologist; he must then have realised the limitations of his

own " little patch of immediacy," and have proceeded, as Prof. Whitehead says we must do, to apply the experience gleaned from that patch to the teaching of bygone times.

Be this as it may, the history of epidemiology is replete with illustrations of such lines of thought. Thus it has been suggested that one of the most characteristic marks of pandemic influenza is that it is generally acclaimed by mankind as a " new disease " ; and then, as Dr. Goodall says, and there is no greater living authority on such a point, " There is no such thing as a new infectious disease." The occurrences of 1915-1925 almost seem to justify the application to Influenza of Alphonse Karr's phrase (33), " Plus ça change, plus c'est la même chose," and support the somewhat paradoxical declaration of Hirsch quoted on p. 98. Dr. Creighton's History (9a) suggests similar lines of enquiry. The accounts of the " Sweating Sickness," of " Gaol Fevers, Influenzas and other Fevers of the Tudor period," of " Fever and Influenza from the accession of James I to the Restoration " ; the great opening chapters of the second volume on "Typhus and other Continued Fevers " and " Fevers and Dysentery in Ireland," leading up to " Influenza and Epidemic Agues," in which we are told " Epidemic Agues are joined in the same chapter with Influenzas for the reason that they can hardly be separated from them in the earlier part of the history " ; and then " The only piece of speculation " in the volume, "the disjecta membra of a theory " on " the oldest and most obdurate of all the problems in epidemiology," that

of influenza, and " the bringing forward in the same context of the strangely neglected history of Epidemic Agues "—this stirring argument was set out by an historian steeped in the medical learning of the earlier centuries, familiar with the life work of Sydenham, Willis and their contemporaries, and with that of the school founded by them, and was critically and appreciatively expounded in relation with the " influenzas," which had appeared under that name upon the stage of history during subsequent years. Creighton's facts and speculations stirred the minds of his readers between 1894 and 1915, and made them more apt to receive the impressions hammered upon them during the then succeeding years.

Already in the early " nineties " Franklin Parsons (45a) had laid stress upon the types (pulmonary, cerebro-spinal and gastro-intestinal) of influenzal prevalences; moreover, Leichtenstern (34) urged, then, that " Influenza presents at least two phases, one pandemic and the other endemic, and they follow different epidemiologic rules "; he further expressed two beliefs—first, that " trailing epidemics show diminished morbidity, less wide geographical distribution, scarcely recognisable communicability, slow development and extension and continuous diminution in frequency and intensity "; and, second, that " in the later epidemics the *vis morbi* becomes more pronounced with the decrease of the *vis contagii*, owing perhaps to weakened influenza germs entering into closer symbiosis with other pathogenic organisms."

Again, Dr. Goodhart (22) declared, in the middle of the "nineties," "influenza is still with us"; and it was becoming recognised that in family attacks of influenza the disease was apt to be quite differently manifested in the several sufferers, and, if this was accepted as regards households, Why, it was being asked, was it not credible as regards communities also? In E. Herts, in 1904-5, Dunn and Gordon (13) described their "obscure disease simulating influenza"; then came the cerebro-spinal fevers of Glasgow and Belfast, and prevalences reported upon by Brorström (3) in Sweden and by Farrar (17) and Reece (49a and b) in this country, and the great poliomyelitis of New York (44) in 1916. In London, Shirley Murphy, more than twenty years ago, secured the notification of cerebro-spinal fever and soon afterwards of poliomyelitis and polioencephalitis, and Borough Medical Officers made careful study of each case notified. At a meeting of the Epidemiological Section on January 26th, 1912 (p. 94) it was thus possible to assure Dr. Reece, of the Ministry of Health, that, in London, cerebro-spinal fever and poliomyelitis were distinguishable from one another by reason of the fact that one set of records was on blue forms and the other set on white forms. In the London Annual Reports for 1914-1917 (25s, 3) account of the behaviour of these two epidemic diseases was given, and in 1915 study of the close relationship between cerebro-spinal fever and influenza in London was made. Then came the great pandemic and early in 1918 (Ann. Rep. for 1917, p. 2) it was stated that "The events of the last few months once more strikingly

illustrate the 'posting character,' the unexpected manifestations and 'the protean behaviour of influenza'; and, incidentally, the close connection, between polioencephalitis (i.e. the disease shortly afterwards called encephalitis lethargica), poliomyelitis, cerebro-spinal meningitis, and influenza, seems to be established."

Some months later, in a special report (25j) the position was thus described, " Taking into account so far as may be, variations of fashion as regards nomenclature, there seems to have been, round about the time of the great pandemic influenza, increased mortality from cerebro-spinal fever (and it may be added from polioencephalitis and poliomyelitis also), from some five or more years before, to some five or more years after 1890; in the same way for five or more years prior to the explosion of 1918 there was again a growing diffusion of both cerebro-spinal fever and poliomyelitis. There has thus been an overlapping of outbreaks of cerebro-spinal fever and poliomyelitis with the great prevalences of influenza. The former precede and lead up, as it were, to the pandemic prevalence; with the establishment of this, cerebro-spinal fever and poliomyelitis fall into the background, but later again come to the fore, as successive 'trailers' follow the great prevalence; five or more years after the pandemic they revert again to comparatively speaking insignificant proportions."

The events of the last nine years have confirmed the correctness of this account when applied to recent epidemiological happenings. It must be noted, however, that " encephalitis lethargica " has been much more

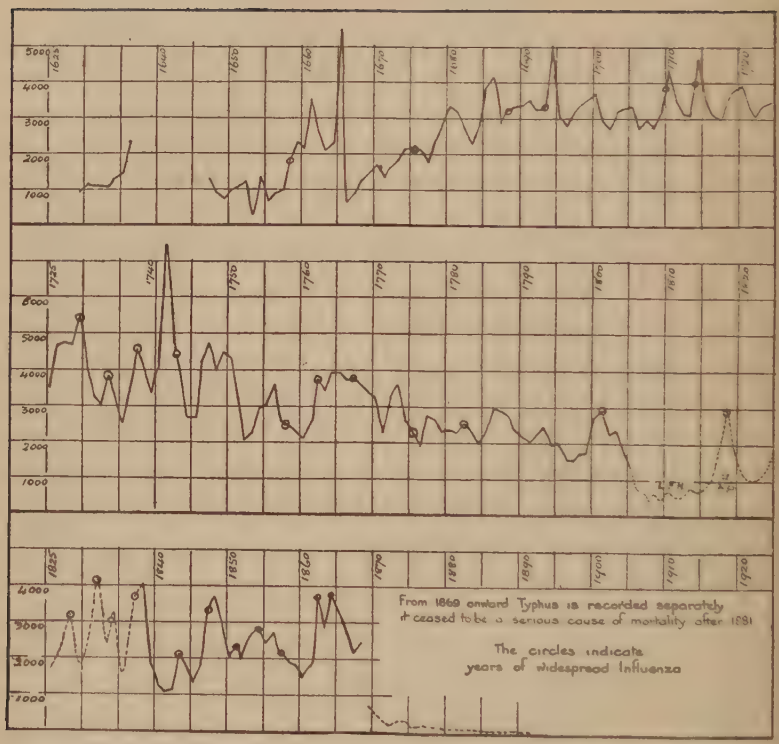
favoured as an appropriate description of the cerebro-spinal types of influenza in those years than had been the case in the "nineties." A discussion of the probable relationship between encephalitis lethargica and the other nervous types of influenza appeared in the London Annual Report for 1920 (25s, 4, 20-21). As has been already shown, encephalitis lethargica can be traced back at least as far as the fifteenth century in England. An account of the contrasted points of view, of the "nineties" and of 1918, with regard to the disease, is given by Crookshank in his paper on "The Theory of Influenza" (10a, p. 463).

In the Ministry of Health Report of 1920 (38a), Sir George Newman gave (p. xvi) an account of "our growing experience of the setting of an influenza epidemic"; and the same report sets out in detail the experiences of John Huxham between 1728 and 1752, and presents a summary record (p. 17 and onwards) of similar phenomena collected by various observers, from Sydenham's time down to 1847. This question of "setting" (to quote Sir George Newman), compels direction of attention to the epidemiological record and to the form of the epidemic wave; and it may be well, therefore, again to pass in review some of the salient points arising in these connections.

The diagram shown as a frontispiece to this volume gives the statistical record of the Evolutionary development of the Influenzal Constitution. The prevalences of epidemics belonging to the Influenzal family appear in their time relationships, beginning with the English

Sweats from 1485 onwards, which were preceded, accompanied or followed by Convulsive Ergotism or "Kriebelkrankheit," epidemic agues, "volatile typhus," encephalitis and "brain fevers." Influenza appears first under that name in 1743, typhus in 1760, relapsing fever and dengue about the same time. Then in the nineteenth century come the dates of birth of cerebro-spinal fever, the Heine-Medin group of diseases, and poliomyelitis—that of the newest disease, encephalitis lethargica, occurring only some ten years ago. Relapsing fever and typhus, and the Heine-Medin group of diseases were (from the original use of those names) recognised as standing in very close relationship with one another, if not with influenza; while for two hundred and fifty years, at first by a few far-seeing observers, then by an increasing number of "annalists," since 1847 by Peacock and since 1890 by Franklin Parsons and others, the three types of influenzal prevalences have been clearly envisaged and described. It is of interest to find lethargy occurring in 1658 in Copenhagen contemporaneously with the epidemics described by Willis in Oxford and London; and to compare together Sydenham's "coma with absolute aphonia," Butter's "acute fever with dumbness," the "Nona" of the nineties and the supposed "new diseases" of Netter and von Economo. In Epidemiology, the question may well be asked, What's in a name?

The London Bills of Mortality (p. 138) give statistical expression to the "settings" of influenza in the eighteenth century; we see the sudden universal colds appearing on the crests of three to six year waves of fevers.

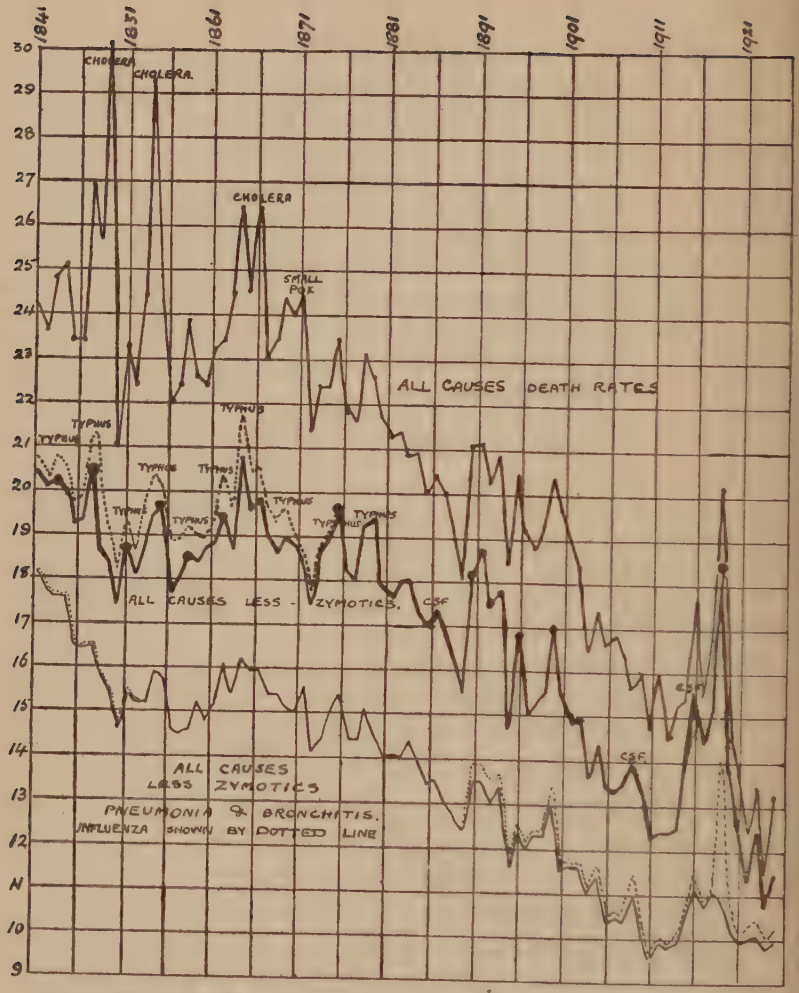

From 1869 onward Typhus is recorded separately & ceased to be a serious cause of mortality after 1891
The circles indicate years of widespread Influenza

London Deaths from Fevers, 1629-36 and 1647-1804, with Estimated Deaths, 1805-1838 (deduced from London Fever Hospital or Glasgow Infirmary records), and Registered Deaths, 1839-1869, showing the "setting" of Influenza on the crests of waves of fevers.

After 1750, as Dr. Gee used to tell us, " pneumonia " changed its meaning, and about then both " influenza " and " typhus " made their appearance. The Registrar General's Reports (p. 140) enabled the story, made clear by the London Bills to be followed up into modern times. From the " all causes " rate we can take out the " zymotics " and then are left with undulations resembling those of the fever waves of the eighteenth century. From these figures in turn, we can take away bronchitis and pneumonia, and we then see that a residual undulatory curve still remains. From the " forties " to the " eighties " the waves swell and subside in correspondence with recorded prevalences of typhus and then, after the " nineties," in association more particularly with influenza and epidemic diseases of the central nervous system.

The diagram on p. 71 throws further light upon nomenclature changes. The contours there show actual deaths, not rates. The scale for " all causes " is one-fifth of those for " zymotic diseases " and " bronchitis," two-fifths of the scale for other causes. Note the great decline in all causes and phthisis, the decline in bronchitis, and the rises in " diseases of the circulatory system " and " cancer." Note especially the steady decline in zymotics and the apparent sudden development of pneumonia and influenza after 1890 (25i, 10, pp. 15-24).

Brief reference must also be made here to study of the form of the epidemic wave, from the time of Farr to that of Ransome, Ross, Brownlee and others. Shirley Murphy's work, moreover, on " school influence " from the " nineties " onwards, exercised much influence.



London Death Rates, per 1,000 population, in registration times, illustrating the appearances of Typhus and Influenza on the crests of waves of fevers. The black circles in the graph for "all causes, less zymotics," indicate influenza years.

Brownlee's first paper on the general question was read before the Epidemiological Section, Royal Society of Medicine, in May, 1909; see also paper of February, 1918; an account of an important discussion arising between Ross and Brownlee and of a later very interesting discussion arising between Brownlee and Spear may be referred to (25i, 5, ii). As already noted, the type to which the London measles wave conforms was considered in 1906 (25h). See also 25s, 1 (1912, Diagram D, between pp. 154 and 155).

The diagram (on p. 11) shows the measles wave (of eighteen months to two years' in length from crest to crest), the type of which is practically determined by number of " effective susceptibles," of whom some 2,000 are added weekly, and thus the total " effective susceptibles " ranges from about 120,000-180,000. While the type of the wave is thus fixed, the tendency to occurrence of seasonal maxima, in April-May and December, appears to be intimately associated with aggregation of children in schools (25s, 2, Diagram H and p. 199). The seasonal waves of scarlet fever and diphtheria in New York, Paris and London, stand in marked contrast to that of measles, and also differ notably from one another as regards times of maxima (25s, 4, pp. 84 and 85).

In Influenza the numbers of " effective susceptibles " above quoted for measles would need to be multiplied, say by five and, for influenza in pandemic phase, the time scale would have to be reduced to about one-sixth of the measles scale. Comparing such a *theoretical* with the *real* influenza curve, it becomes clear that the virus

here is *variable*, not *stable*, as in measles. The wave lengths in influenza in fact range from about one-third to two-thirds of a year in pandemic times, to some five to seven years in the troughs between pandemics. The recognition, that such is the case, necessarily carries with it full acceptance of the truth that influenza in London is an *endemic* disease.

Study of the epidemiological record has, then, made it clear that, so far as the influenzal group of diseases is concerned, the natural history method, the method of Hippocrates, is that which must primarily be relied upon. Dr. Adams tells us that it is very difficult to assign the cases described in the first book of the Epidemics of Hippocrates to their appropriate disease categories. The reason he says is, that they are "directly drawn from Nature." Sydenham followed this method, and Dr. Payne not many years ago remarked that it is sometimes impossible to decide as to the nature of the prevalences he is discussing. Nowadays, we are very prone to think in terms of "causal organisms" (as we used to call them; they are really many of them, just "associated organisms"); whereas Sydenham and his followers unravelled the relationships between *associated prevalences of epidemic diseases*, and we are beginning to realise that it behoves us, too, to think in epidemics as well as in micro-organisms.

The outcome of all this may be best appreciated by focussing attention upon Sydenham's treatment of the difficulties with regard to Influenza; but it must be a reversion to Sydenham's matured conclusions, not

merely to the tentative and, as would now appear, somewhat prematurely conceived doctrines enunciated, in those wonderful opening chapters of his Medical Observations, in 1676. This early draft, as has been seen, underwent in Sydenham's own mind a considerable amount of revision; the sketch (incorporated in the edition of 1676), achieving as it soon did, a world-wide reputation, has perhaps not unnaturally been commonly regarded as representing his final view; examination of the development of the conception as revealed in the writings of the older Sydenham will, however, show that this was very far from being the case.

Already in 1676 (Med. Obs. V, vi, 6) it appears he was beginning to concern himself with what may seem a somewhat meticulous enumeration of differentiæ between the "stationary fevers" of his earlier constitutions; and, even at that date (V, v, 1-3 and V, vi, 1-2) he noted the resemblances of his first stationary fever to that of the winter of 1675, to which, and to the successors of which, he makes fuller reference in the Letter to Dr. Brady of 1680 (paras 54-57). At about this time a possible solution of his difficulties seems to have been dawning upon him. One never need feel surprised at coming across some new light in studying Sydenham, and it is not to be wondered at, therefore, that a pearl of great price is to be found hidden in, what is at first sight, a somewhat unpromising *Postcript* (to his *Tractate on Dropsy*) written in 1685; here, after two and a half centuries, we can still glimpse one of his flashes of inspiration; it relates to an epidemic following after that

intriguing fever of 1675 already alluded to above. He has pondered over this and its successors, and especially over the prevalence of 1679, which has been hailed by modern epidemiologists as an influenzal trailer. He was after a year or two led formally to abandon (and he thought it well to place the fact upon record in the postscript to his newly published work), the impression he had at first entertained, that this fever of 1679 was something new. He says it must be reckoned as a common "intercurrent," and he styles it the "winter fever"; then later still (Sched. Mon. 1, 4) he explains that, while at first disposed to regard this "winter fever" as just an "intercurrent," i.e., as "a bastard peripneumony which occurs in all winters alike," he now realises that it is entitled to rank as a stationary fever; he proceeds, therefore, to execute a full length portrait of this addition to the family (Sched. Mon. 1) and there it stands, an unmistakable example of a cerebro-spinal influenza of the seventeenth century, of which the London cerebro-spinal fever of 1915 was, as was claimed at the Royal Society of Medicine at the time, an indubitable lineal descendant (25k). In the final paragraph of Sydenham's account (Sched. Mon. 1, 46) he has another inspiration, for he says of this stationary fever, "it may be a spirituous and subtle beginning of something else, the germ perhaps of the depuratory fever now exploded, but which the plague followed." Of course, as we now know, it was the precursor of the influenza of 1688, just as the London cerebro-spinal fever of 1915 was the precursor of the great influenza of 1918.

The new light afforded by demonstration of the relationship of this fever of 1685 to the succeeding influenza ; and especially the clear recognition, which has just been noted, by Sydenham, of the possibility, nay likelihood, that this 1685 fever was identical with the stationary fever (" depuratory fever ") of 1661-4, in which he had been so greatly interested nearly a quarter of a century previously, enable us step by step to trace the development of his maturing view (which has been already glanced at on p. 97) that the standard fever of 1661-4, that of the winter of 1675, the depuratory fever, the " winter fever " of the *Postscript* of 1685 above referred to, the fever of 1685, and we must now add the influenza of 1688 (though that was the year of Sydenham's death), were all phases of one abiding influence. There is here, in fact, as already pointed out, pp. 94 and 142, the germ of the modern conception " endemic influenza," and it is especially interesting, therefore, to find " endemic influenza " clearly identified by Sydenham with the stationary fever of 1661-4, and thus forming part of the " setting " of the great influenza of 1658 described by Willis (66a, 2) in the chapter spoken of by Creighton as constituting the " first piece of Epidemiology written in England." Moreover, we realise that Sydenham, shortly before the close of his life, did in fact witness the completion of one of the cycles of epidemics which he had prophetically referred to (M. O., I, ii, 23), when he wrote of "posterity being able to take the full view of the whole cycle of epidemics in their mutual sequences for years to come."

In recent discussions regarding Sydenham's Constitutions at the Royal Society of Medicine, while there has been some difference of opinion on the general questions at issue (i.e., with regard to Sydenham's theories enunciated in the Medical Observations in 1676) there has been practical unanimity concerning the special application of his thesis to epidemic prevalences associated with influenza. It may be of interest, therefore, at this stage, briefly to summarise the main points of resemblance between twentieth century findings concerning the influenzal constitution and the conception already envisaged two and a half centuries previously by Sydenham.

In the *first* place stress must again be laid upon Sydenham's account, alluded to on pp. 86 and 92, of his fifth constitution (that of part of the year 1673 and of the whole years 1674 and 1675) which is now recognised as the original classical description of an influenzal constitution. It comprehends a widespread influenza occurring, to use Sydenham's terminology, in a setting of "comatose fevers." This series of prevalences quite plainly furnishes the almost exact counterpart of the great influenzas of 1918 with their precursors and trailers. Thus, following upon comatose fevers in 1673 and 1674, we are told, the fever of 1675 "spread its ravages far and wide" in July (exactly, it may be noted, in passing, as it did in 1918); the attack was first upon the bowels and then the head, the fever, however, "having the predominance and taking the lead of the other maladies of the year."

At the end of October the weather "suddenly changed to wet and cold. This brought on coughs and catarrhs, which" (says Sydenham) "were more numerous than ever I remember them to have been," and upon these "supervened the stationary fever of the year (as in October-November, 1918) and this, having once taken its hold, increased, and varied in some of its symptoms from the fever of the previous part of the year," attacking, however, now the lungs and pleura instead of the head and bowels. At the end of November the catarrhs and coughs suddenly decreased. "The fever, however, remained as before, just as it was before the catarrhs" (V, i, 7). "All that suffered, suffered first in the head, back and limbs; these being the symptoms" (of the influenza, as we should say, but keeping Sydenham's wording, it reads) "which were most constant to the non-pleuritic fevers, which preceded and which characterised them to their close" (VI, i, 6). Sydenham's description is unmatchable for vision, precision and terseness of expression; moreover, he explicitly reiterates, again and again, that while the bowels, brain and lungs were successively attacked, the accompanying diarrhœa, stupor and pneumonia were all merely symptomatic of one and the same fever, and the characteristic marks of that fever he stamps most unmistakably upon it.

In the *second* place it is clear that the pulmonary trailer of 1679 riveted Sydenham's attention upon the special type of prevalence with which the influenzas of the "nineties" made western Europe so familiar; after much study and reflection he concluded that the

said fever recurring winter after winter was identifiable not only with the fever of 1685 (25k), and thus heralded in that "spirituous and subtle something" (the influenza of 1688) but was also identifiable with the "depuratory fever," which had accompanied and been found to be interchangeable with the "intermittents" of 1661-4, (i.e., with the gastro-intestinal, pulmonary and cerebro-spinal trailing epidemics) whch followed the great influenza of 1658.

Then, *thirdly*, there are the phenomena referred to (on pp. 93-96) in discussing transmutations of fevers. We have Sydenham's statement (M.O., V. vi, 2) regarding the interchangeability of the intermittents and the stationary fevers, which "ran parallel with them"; the formulation of the thesis (Letter to Dr. Brady, para. 56) that in intermittents "Nature works hastily and gets over in less time than is regular the processes by which she first tempers and afterwards discharges the morbific matter," while depuratory fevers "are different, thirteen or fourteen days elapsing before the appearance of any signs of the concoction of the febrile matter, which is then to be ejected by sweats, or rather by a somewhat free transpiration"; and the contrast drawn in para. 57, between the later "humoral or earthy fevers, which cleared the blood but slowly," and the earlier fevers of the same constitution, "which were subtle in principle, intermittent in type and (which) did their work more rapidly."

Elsewhere (25p,1) the application to the study of the influenza wave of this mutation theory of Sydenham has

been discussed ; to use modern phrasing, he is contending that the virus of influenza works more easily and rapidly near the crests of the pandemics and with more difficulty and more slowly in the intervening troughs. Furthermore, as has been seen on pp. 86 and 87, there may also be deduced from Sydenham's own writings the conclusion that between the widespread prevalences on the crests of the great pandemic influenza waves and the depuratory fevers (or endemic influenzas) of the troughs, ripples of "intermittents" appear both on the ascending and descending slopes of the great ocean rollers. Sydenham, as is well known, identified the intermittents of 1675-9 (following the great influenza of 1675) with those of 1661-4 (following the great influenza of 1658) ; but he also makes it clear (IV, i, 5 and 6) that similar intermittents preceded both the influenza of 1675 and that of 1688 (Sched. Mon., I, 46).

Thus we may, on Sydenham's authority, complete the two cycles (between the influenza of 1658 described by Willis and that of 1675, and again between that of 1675 and the next succeeding influenza of 1688) as follows :

Willis's Influenza of 1658
Intermittents of 1661-4
Depuratory fevers
Intermittents of 1673-4
Sydenham's Influenza of 1675
Intermittents of 1675-9
Depuratory fevers
Intermittents of 1685-6

and lastly the influenza of 1688 described by Molyneux and Harris. (*See* Table on p. 83.)

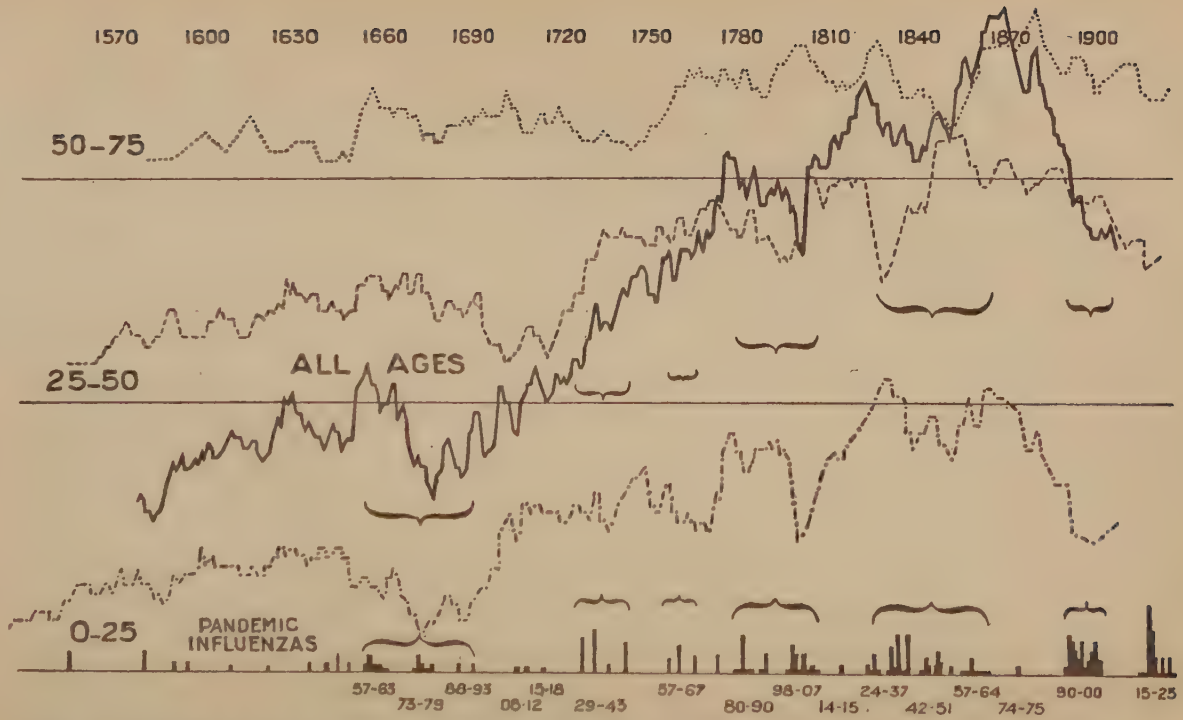
Let us recall his statement made in 1676 (I, ii, 21-23): "I may state at once, that to reduce into classes all the species of epidemics, to arrange them according to their phenomena, to work out their several idiopathic characteristics, to determine in detail the proper method of treatment for each of them, is a work so difficult, an arrangement requiring so much leisure and opportunity, a cycle so little coincident with any recognised sequence of years, that the lifetime of no single physician would suffice for the collection of a sufficiency of data." But he was better than his word, for we find him later adding material contributions, to what (in 1676) he had described as "My mite, such as it is, towards the foundation of a work, that in my humble judgment shall be beneficial to the human race."

As so much has been said and thought recently concerning influenza in its psychiatric relationships, it may be of interest to refer more fully to evidence forced into prominence of late years, proving the damage inflicted by this disease upon the nervous system. The examination of the relation of cycles of genius to prevalences of influenza (mentioned on p. 108) was originally prompted by studies made by epidemiologists of "encephalitis lethargica," and was undertaken with a view to ascertaining whether "influenza years" were periods in which special injury to the central nervous system had resulted. In the first instance the attempt had been made to obtain statistical confirmation of the suspicion that influenza

plays a definite part in the causation of insanity. Precise records of insanity are, however, of comparatively recent date, and the early statistics are so beset with possibilities of misinterpretation as to make the task an exceedingly difficult one; it seemed then to be a more practicable plan to begin, as it were, at the other end, i.e., with men of genius, and to try to ascertain whether the extent to which their nervous systems are damaged by influenza can be gauged with any approach to accuracy.

At first sight it was surmised that the influence, if any, might be expected to be most conspicuously revealed at the age of special intellectual development and of main output of mental work, say at 25-50. On further consideration, it was decided to examine in like manner a corresponding graph for the earlier age-period 0-25. Later still it seemed desirable that the graph for the period 50-75 should also be scrutinised. The three graphs present some resemblances and some noteworthy contrasts.

As they relate to the same lives at different age-periods, in youth, in early and in late maturity, respectively, it is obvious that the three contours will show a considerable degree of resemblance. For example, the 25-50 graph for the years 1675-1735 must, so to speak, mimic the 0-25 graph for the years 1650-1710; and similarly the 50-75 graph for the years 1700-1760 should roughly correspond in outline with the corresponding portions of the 25-50 and 0-25 graphs just referred to. Obviously, however, the 25-50 graph will lose some of the years of life (which it might have been expected to have



Years lived through by men of genius, in relation with periods of great Influenza prevalence. The base lines of the graphs representing years lived at 50-75, 25-50, and 0-25 years, are just below the corresponding figures on the left of the diagram; that of the graph for All Ages is identical with the lowest of these three base lines. The figures at the foot of the Diagram are dates of Influenza prevalences in successive centuries from the sixteenth to the twentieth.

credited to it) owing to early demise of individuals counted in the preceding 0-25 graph; and, again, greater losses still will accrue in the 50-75 graph, owing to the higher rates of mortality at ages 50-75 than at ages 25-50.

On examining the special effect of groups of "influenzal years" it is at once apparent that they operate prejudicially in all three graphs, though their evil influence is easily most discernible in the 0-25 graph. It is especially to be noted, however, that evidence of this influence is not blurred, but is, indeed, on the whole, seen to be more pronounced in the graph for all ages.

The marked influenza periods of the last three centuries: 1657-93, 1708-18, 1729-43, 1757-67, 1780-90, 1798-1807, 1824-37, 1842-51, 1857-64, 1890-95 and 1915-1925, were examined seriatim to ascertain the depth of the depressions produced at these times in the outlines of the graphs for 0-25, 25-50 and 50-75 years of age respectively. In the case of each depression the depth of the lowest point, below the mid-point of a line joining the crests on either side of the trough between two adjacent waves, was expressed as a proportion of the height of the aforesaid mid-point above the base line of the graph. Thus an *index* for each depression was obtained representing the proportion of loss, per number of lives at risk, for each group of influenzal years.

This index of brain injury (as it may be termed), inflicted by each influenzal prevalence, was found to vary from practically *nil* in three instances, viz., the 25-50 graph during the influenzal periods 1729-43 and 1842-51

and the 50-75 graph for the period 1757-67, to the *highest limits*, of two-fifths for the 0-25 graph in the period 1798-1807, of half for the 25-50 graph in the period 1824-37, and of rather more than half for the 50-75 graph in the period 1842-51. (It will be noted that, as might perhaps have been anticipated, these three deep troughs follow one another at approximately twenty-five year intervals). As a rule, the range of the indices is about one-twelfth to about one-third. The average of all the indices, for the 0-25 graph, approaches one-quarter; for both the 25-50 graph and 50-75 graph about one-eighth; while the average for the combined graphs is nearly one-quarter.

The question at once arises whether these indices are approximately of the magnitude which might have been expected *a priori* in dealing with *any* epidemic disease causing mortality among, and incidentally influencing output of work by, men of genius?

This question may be elucidated as follows. The London Bills of Mortality show, as has been seen, "epidemic colds" or "universal fevers" on the crests of fever waves; in Registration times like phenomena can be discerned between 1837 and 1874-5, then comes a long interval, to be succeeded by influenza years in the early "nineties" and again from 1915-25. Study of these two charts makes it clear that the question of the last paragraph must be answered in the negative. In the first place, no epidemic disease, of which precise statistics are available, causes such ravages as are shown, in these graphs, in years of prevalence of the influenzal group of

diseases. Limiting consideration, then, to that group, the greatest recorded *rate of mortality* for the population as a whole was that of 1918. The total London loss from influenza in that year was about 18,000, rather more than one-fifth of the total deaths registered. So high an " index " as this was not forthcoming in any earlier group of years, though the *proportion of total deaths to population* was equally high, in two individual years of special influenza prevalence, during the middle third of the eighteenth century; the average index, however, taken over the whole of the prevalences of the last 250 years, was clearly very much less than one-fifth.

It is hence apparent that the influenzal groups of epidemics leave their impress to a quite excessive extent upon brain workers as compared with the population as a whole. It was, in bygone times, almost a commonplace that sweat, influenza and " volatile typhus " affected " gens aisés," " people of the court " and the " noblesse," in contradistinction to other epidemics which specially attacked the poor, badly-housed and ill-nourished. Fracastor (19), speaking of his fever with spots like flea-bites, carefully discusses the reasons for this preferential incidence upon the well-to-do, whereas plague attacked the poor. He says, " From that contagion, therefore, which spreads from one person to another, the well-to-do are able to guard themselves, by reason of facilities at their disposal which common people lack, but from that contagion, which is communicated through the air, the well-to-do are less able to protect themselves than the poor are, for that which may affect all alike does affect

those who are more delicate and less robust, more full-blooded and more humid, on account of their luxury and quiet mode of life. The people, on the other hand, are more robust and less humid, as being harder worked and of more sparing way of living."

One reason for this excessive class incidence may have been that those who used their heads were more liable to suffer than those who used their hands. We must, in fact, accept the conclusion that the widespread prevalences of influenza during the last two and a half centuries have levied a specially heavy toll upon men of marked ability; and in some conspicuous instances the facts are on record that the influenzas of past times again and again attacked certain notable men and women. Chopin, Sterne, Swift, Jane Welsh Carlyle, and William James, may be referred to as instances of this, and for the abrupt termination of the lives of many remarkable men (from Shakspere and Cromwell onwards) influenza was presumably responsible. Again, in quite recent years, it has been shown that, in the case of children and young adults, the cerebro-spinal precursors and trailers of influenza are a source of great damage to the central nervous system. It is a significant fact that the baleful influence of influenza thus seems to be particularly exhibited upon the newly-born, or upon quite young children, and this conclusion is borne out when the names of men of genius are plotted out according to their years of birth, for there is discernible a tendency for such men not to be born during years of severe prevalence of influenza; this, of course, tallies with the fact that

miscarriages and stillbirths increase at such periods; but the further question arises, whether many of the infants then surviving may not be handicapped by damaged brains.

The critic may urge that, while appreciating that something may be said for approaching the study of Epidemiology from the "Big Endian" as opposed to that held during the last quarter of the last century, which may perhaps be termed the "Little Endian," point of view, he would like to know whether it is likely that anything of *practical* value will result from adopting this method of approach, say, for example, in the case of influenza. Certain conclusions may at any rate be drawn. Influenza is, as Noah Webster said years ago, the "crux of epidemiology." It is not merely, as it was long supposed to be, a "pandemic disease" re-appearing once or twice in a generation, but it is ever present, now smouldering and then, every ten, fifteen or twenty years, bursting into flame. Its great prevalences are especially favoured by war, famine, overcrowding and free communication with sufferers from the disease in the early stages of their illness. Despite, however, the huge increase of means of intercommunication and traffic during the last one hundred years, coupled with entire absence of systematic attempts to limit spread of the disease by sufferers in the early stages of illness, the mortality in the London of to-day from the influenzal group of diseases appears not to be appreciably greater in proportion to population than it was nearly two centuries ago. The influences that have made for good

have been improved feeding, better housing, greater cleanliness and provision of medical and nursing care in serious cases; but now, while continuing to develop resistance on these lines, *there should be added thereto*, carefully considered measures for preventing sufferers from mixing freely with their fellows in offices, schools, conveyances and places of assembly, as they do at present while in the early highly infectious stages of illness; above all, it must be appreciated that the most extravagant and bizarre efforts made, under the influence of panic, at times of widespread prevalence, are as nothing compared with steady and continued prosecution, year in, year out, of a considered campaign, against the influenzal group of diseases, conducted on epidemiological lines.

The conclusion from a survey of the last century of Epidemiology, would then appear to be that reached by a number of Chadwick lecturers. It was first stated, however, by Sir Wm. Collins (7c), in a form in which it is particularly applicable to Epidemiology, in an address on "Physic and Metaphysic," delivered to the Abernethian Society on February 16th, 1905. Sir William, quoting Dr. Martineau, says, "Laplace, in scanning the heavens with his telescope, could find no God, and Lawrence declared that the scalpel in dissecting the brain came upon no soul. Both are unquestionably true and it is precisely the truth of the second that vitiates the intended inferences from the first. Had the scalpel alighted on some perceptible soul we might have required of the telescope to perform a similar task; and on its bringing

in a dumb report have concluded that there was *only mechanism there*. But in spite of the knife's failure, we positively know that conscious thought and will *were* present, but no more visible yesterday; and *so* that the telescope misses all but the bodies of the universe and their light avails nothing to prove the absence of a living mind through all. If you have the wrong instruments the objects of your search may well evade you. The test tube will not detect an insincerity or the microscope analyse a grief."

This question of instruments assumes, nowadays, very great importance in connection with epidemic disease, epidemiologists using field implements sometimes glean very different conclusions from those deduced by bacteriologists employing laboratory implements. As a striking case in point, "food poisoning" may be referred to. The epidemiological evidence has gradually accumulated during the last three and a half centuries. Dr. J. J. Walsh (61) carries us back to the food poisonings of the Middle Ages, which, he says, were in the main cases of illness (often apparently of infectious illness) with obscure abdominal or cerebro-spinal symptoms; and thus the characters of those supposed "pitiless poisoners," the Borgias, were taken away, owing to failure to recognise the symptoms of gastro-intestinal and cerebro-spinal influenza. Ozanam also testifies that epidemic encephalitis was often regarded as due to poisoned food. Crookshank (10a, 3-7) has carefully set out the evidence for acceptance, as cerebro-spinal influenza, of much of the "convulsive ergotism" of past centuries.

Even as recently as 1888 we find the Middlesbrough outbreak of pneumonia ascribed to food. Leichtenstern, however, spoke confidently of "influenza dinners" in the early "nineties," and Bulstrode's report on the Greenwich outbreak of 1893 was typical of many others in which influenza (and not food) was presumably at fault.

But the whirligig of time brings in its revenges and many supposed food outbreaks of the "nineties" were accordingly studied exclusively from the bacteriological point of view; again, during the recent influenzas, botulism ran riot in the Western States of America and both here and on the Continent large numbers of reports on food outbreaks appeared, in which "causal organisms" (complying with appropriate serological tests) were described and exhaustively studied, from many points of view, but not from that of possible association with the prevailing epidemic.

In a recent report (37) mention, however, is made of "a considerable number of cases which are ascribed, often very confidently, to food poisoning without any justification." Moreover, we learn that "Medical Officers and others have sometimes limited their interest and activity to tracing the outbreak to some given article of food," while "the more distant sources have been left untraced"; even in the Report in question oddly enough, no mention is made of influenza, though the survey relates to outbreaks, occurring during years of widespread prevalence of that disease.

The records of these recent years, in fact, abundantly bear witness to the need for field observations and field

research having place, as well as laboratory observations and laboratory research, the two sets of findings being placed alongside one another and co-ordinated together. Given such a consummation, it may be surmised, that in public health, as in other branches of enquiry, an "Age of Professionalism and Specialism" will slowly but surely give place to an age in which interest will be taken in general principles as well as in stubborn and irreducible facts. This is the lesson, which he who runs may read, in the History of Epidemiology during the last hundred years.

And now having ascended this steep and stony track, leading "upwards all the way, yes, to the very end," a glance may be cast over the ground recently traversed; beginning at a point, say like that described nine years ago (25m, 1, p. 72), when the hope of gaining a very imperfect inkling of what Sydenham might perhaps be driving at with his epidemic constitutions, was for the first time entertained, and when the belief was perhaps even held (l.c. p. 73) that the upward continuation of the path was plainly in sight; then later, advancing to the stage (25m, 2, p. 182) where the possibility dawned upon the mind that something might be found a few yards further up, a piece of presumption which of course evoked the warning, that achieving what looked like the summit would bring complete disillusionment for the simple reason that there was nothing there; then at long last the cairn erected two and a half centuries ago by Sydenham stands revealed to view. Something like this, surely, has been the experience of many an

epidemiological pilgrim, who has let his treasured roll fall from his hands midway up the "Hill Difficulty," and has then, perforce, retraced his steps, recovered his precious roll and comforted by it, been enabled to complete the ascent.

A beautiful piece of work cannot, it is said, be appreciated until we have actually walked in the steps of the man who produced it, and this truth seems to hold, for negotiating the path up this particular "Hill Difficulty." Sydenham plainly marked out, however, the way to be followed, and those who are minded to tread, *literally*, in his footsteps, may, at least, enjoy an exhilarating climb. Perchance the supposed imposing eminence is, after all, just a foothill, giving approach to a succession of rock climbs ascending to heights unscalable by present-day mountaineers, but the preliminary scramble is well worth while for its own sake, and those who accomplish it may add, each one, his pebble to the pile of stones built long ago by the Founder of Epidemiology, the maker of the original ascent.

IN RETROSPECT

Looking back over the ground traversed, it is clear that the clue to threading the mazes of epidemiology is that used by the clinician attempting to bring within his "unity of apperception" the varied impressions passing through his mind as he scrutinises his patient. Success, in the one form of adventure as in the other, depends largely upon the ability of the diagnostician to draw upon experience of many epidemics, or of many individual examples of disease, as the case may be; indeed, it is only when a sufficiency of reminiscences has crossed the threshold of his mind that the psychological moment arrives, when he becomes at length equipped for giving a local habitation and a name to the special instance before him. This truth has been illustrated in the foregoing chapters; by examples from the groups of prevalences, contemporaneously occurring in various parts of Europe, in the fifteenth and sixteenth centuries, at the time of the English sweats; by reference to Willis's outbreaks of 1657-8, now known to have appeared coincidently with epidemic lethargy in Copenhagen; by studying, too, Sydenham's minute and circumstantial account of his Constitutions.

In 1749, Dr John Swan, Sydenham's translator, had pointed out (p. 520) that "Truth and nature being always the same, to be convinced of the variety of systems we need only attend to the vast number that have been

invented and the revolutions they have all undergone. Those, which prevail at present, were either not invented fifty years ago, or at least were little or not at all followed at that time, though it must be allowed that nature was the same then as she is now; and doubtless these will meet the same fate with those that have gone before them." Dr Swan was presumably basing this judgment upon findings such as those of Rogers, Huxham, Rutty, Wintringham, Hillary, Strother, Butter and others, whose descriptions are referred to by Creighton, in his "History of Epidemics in Britain," where they may be compared with corresponding Continental accounts given of Convulsive ergotisms, Picardy sweats and Italian and German miliaires and purples (see also Creighton's translation of Hirsch). In the nineteenth century there were added to these records the writings of Clutterbuck and Mills and later of Jenner and Stewart in this country, of Graves and Stokes in Ireland and of European and American clinicians and pathologists. All this later work drove home the correctness of Dr Swan's view, when he added, to his note above—"Upon a close enquiry it will be found that most of our real knowledge of nature is the result of observation and experience only; but as to the manner of accounting for her operations, it hath ever changed with the times and will continue to do so; so that little stress is to be laid on it, so far as it is unsupported by fact and by the testimony of the senses."

Within the last hundred years, tropical typhus, cerebro-spinal fever, poliomyelitis and encephalitis lethargica have emerged into the nomenclature and

for some time past steadily increasing significance has been attached to pathognomonic signs and to the presence of associated micro-organisms. Perhaps the most instructive lesson of the whole epidemiological history is to be drawn from contrasting the diversities of judgment as regards diagnosis, between Sir William Jenner (32, 3), with his three clean-cut continued fevers and his " non-contagious and sporadic (but now and then) epidemic " febricula, and the less precisely defined but perhaps more epidemiologically correct view of contemporary Irish physicians, faithful followers, all, of the method of their master, Sydenham. In the first passage cited Sir William explains that any clinician " who looks over a list of the diseases other than the acute specific diseases, under which patients were labouring when received into a fever hospital with certificates from a medical man that they were affected with fever," will recognise at once " that the diseases are referable to two classes." He includes pneumonia and intracranial inflammations in the first class and febricula in the second. We have seen how Sydenham dealt with *prevalences*, of pneumonia, intracranial inflammations and febriculas, preceding and following his influenza of 1675. Drs. Graves and Stokes, as pointed out elsewhere (25n, p. 73) also took the broad view of these epidemiological relationships. Sir William Jenner, on the other hand, does not refer to influenza and inferentially draws a line of demarcation between his three continued fevers and influenza and any prevalences associated with it. It must be recognised, nevertheless, that the closely delimited outlook of three-quarters of a

century ago, reminiscent though it be of the "blinkers" shutting out the view on each side of the horse's head, stimulated the advance of knowledge, by concentrating attention for the time being upon the piece of road then being traversed and so enabling followers of the great clinician and pathologist to extend their acquaintance with the behaviour of the continued fevers, during a period which chanced to be one of slack water between two great tides of influenza prevalence. Moreover, thanks to this preliminary work and to the ever growing facilities for epidemiological study forthcoming in later years, it was possible under favouring modern conditions to make a more adequate *Weltanschauung*, of the pandemics of the "nineties" and of 1915-25, than would otherwise have been the case.

Thus Sir William Jenner's *Lectures* have come to possess a peculiar interest for the student of the history of epidemiology. In the first lecture, on the "Identity or non-identity of typhoid and typhus fevers," he refers (p. 90), to cases described by M. Landouzy in the prison at Rheims, and he says: "To show that petechiæ, diarrhœa and delirium were present during life in a number of cases and that some lesion of the intestine was found after death in the same cases, is by no means to prove that these persons died of typhoid fever." He refers to the frequent complication of typhus with dysentery, and adds in a footnote that M. Landouzy "appears to have had in the prison at Rheims, cases both of typhus and typhoid fevers." He continues: "The presence of petechiæ by no means proves that a case is not typhoid

fever. Petechiæ may occur in scarlet fever, small-pox and in many other diseases (as all who have witnessed much of these affections will readily allow), when the patients are placed in unfavourable circumstances, and occasionally even under other conditions. There is no proof that the mulberry, or true typhus, rash was present in M. Landouzy's cases, or that true rose spots ever passed into petechiæ ; nay, it is even within the range of probability that some of the so-called petechiæ were really flea-bites. Similar circumstances favour the spread of typhus and typhoid fevers. The poison of both appears subject to the same laws of development ; therefore, where one exists the other is likely to exist." . . . "The same confusion, from the same cause, exists in the descriptions of typhus fever by the writers of our own age, who have not drawn the distinction, which nature has, between typhus and typhoid fevers." And then he proceeds : "The attempt to settle the question of the identity or non-identity of these diseases by a reference to old writers appears as absurd as it would be for astronomers of the present day, with eyes in their heads, telescopes in their hands, and the heavens above them, to found their opinions respecting the movements of certain celestial bodies on the dicta of Ptolemy or the observations of Copernicus."

In his third Goulstonian Lecture of 1853 (p. 450) Sir William Jenner recurs to this difficulty of reconciling "the histories left us of the various epidemics of fever, that from time to time have swept over large portions of this and other countries" . . . "with the idea of

the specific individuality of typhus fever, typhoid fever and relapsing fever." And then follows the notable passage which has been already alluded to on p. 100.

These perplexities, experienced by Sir William Jenner seventy-five years ago, were last year adduced (25 0, 1 and 2) as illustrative of difficulties such as those experienced by Graves in interpreting the occurrence of gastric, cerebral and even pulmonary symptoms " in the worst forms of typhus " ; such as those of Sydenham in accounting for petechiæ, purple spots, etc., in his " new fever " of 1685, and those of Farr in explaining the association of prevalences of typhus and of influenza in 1847.

Moreover, further " obstinate questionings " arise on consideration of the history, epidemiology and bacteriology of continued fever during the three-quarters of a century which have elapsed since Sir William Jenner's work appeared. Thus :

(i.) There has been a great decline, in countries with hospital and medical services and where, generally speaking, civilised conditions prevail, in mortality from each of the continued fevers of Sir William Jenner. Coincidently, there has been great recorded increase in mortality from influenza and pneumonia, together with notable development of epidemic diseases of the central nervous system ; the latter have been given new names, but they correspond in the main with the prevalences of " brain fevers," " comatose fevers," " lethargies," etc., described during earlier centuries.

(ii) On the other hand, in countries, where war and famine with lack of medical services have prevailed,

" typhus " and " relapsing fever " and, in less degree, " typhoid fever " have behaved much as they were wont to do in years gone by; in certain tropical countries a " tropical typhus " has been described, differing, it is said, epidemiologically from the "typhus" of earlier centuries; moreover, in America, Brill's disease and Rocky Mountain Fever, diseases of similar clinical character, have been observed (Goodall, *Infectious Diseases*, p. 562).

(iii) In many recent outbreaks the infection of " typhus " has been held to have been transmitted by lice (25n, 2); and Rickettsia bodies have been found in infected lice. " Relapsing fever " has been associated in different parts of the world, with bugs and other vectors, transmitting various species of Spirochætes. " Typhus " has also been found associated with Bacillus Proteus X. 19, " believed to be a secondary invader " (Goodall, p. 561). During the last half century the bacteriology of typhoid fever has been perseveringly studied, three or more paratyphoid bacilli have been described and the relationship of bacilli of the typhoid group to the bacilli of food poisoning and to coliform bacilli generally has been much discussed. The bacteriology of influenza, cerebro-spinal fever, etc., too, has been most carefully explored.

(iv) Twenty years ago (25d, 2) attention was already directed to the three special points of difficulty. *First*, that of " persistency of disease types " and of " differences in the germs found in association at one and another time with individual outbreaks "; for example, as was then apparent, reliance upon the agglutination test made it " necessary to assume a multitude of special creations, so

to speak, of causal organisms of meat poisoning—one, in fact, it might almost be said, in every German town, in which an outbreak, which is bacteriologically investigated, occurs" ; *second*, there was "the difficulty presented by the notably profuse distribution of causal organisms without corresponding production of disease" ; and *third*, that of "the failure of the germ theory to explain the close relationship between certain diseases," of which several examples were given.

It may be added, now, that study of recent influenza prevalences, and comparison with those of the middle of the last century, have focussed attention upon the curious fact that three quarters of a century ago little or no consideration was given to the question of possible confusion between influenza (with its related prevalences of cerebro-spinal, pulmonary and gastro-intestinal type) and Sir William Jenner's three continued fevers. Sir William himself, indeed, makes only one casual reference to influenza (on p. 440 of his great work. See 25 0, 1). Murchison, on the other hand, was fully alive to the danger of confusion, so far as cerebro-spinal fever and typhus were concerned. The recent epidemiological history, of course, contains frequent references to similar sources of risk. The new light thrown, by the two recent pandemic prevalences, upon influenza and continued fevers strikingly illustrates the truth of Dr John Swan's dictum that "the manner of accounting for Nature's operations has changed with the times."

It seems at least clear, however, that conditions of war, famine, and accompanying ills attendant thereon, play an

important part in modifying most of the disease types now under consideration. This was made abundantly evident in connection with the camp fevers and sieges of historical times and has been demonstrated anew in Eastern Europe and even in this country (see pp. 54 and 56) in connection with certain prevalences of continued fevers in institutions. Again, it seems probable that the *status* of many of the germs associated with these types of disease—i.e. whether the said germs are causal or merely associated organisms and whether the insect vectors transmitting them are necessary factors or merely play a subsidiary part in facilitating spread of infection—is by no means, as yet, precisely understood. Moreover, the laboratory findings have as a rule been worked out in a much more complete way in sporadic cases than in the great epidemic prevalences, and it is very interesting to note, for instance, that some of the investigators of tropical typhus are of opinion, that the disease, while resembling the typhus of history clinically, differs from it epidemiologically. Finally, the laboratory findings throw but little, if any, light upon the epidemiological relationships—upon association of typhus with relapsing fever (discussed by Murchison), or of influenza with the prevalences of its " settings," as described in the Ministry of Health Report.

Epidemiologically speaking, it is of great interest to compare and contrast three ages—that of Sydenham, that of Jenner, and that of Creighton. The first was the age following the Puritan revolution and the early discoveries of the great physicists, physiologists, anatomists and

chemists, and coincident with Newton and the foundation of the Royal Society; it was an age of reaction and in large measure of decadence; it witnessed the great plague and three pandemic influenzas. The second includes the early and mid-Victorian periods, following after the industrial revolution and coincident with great activities of inventors and engineers; the age, too, of Carlyle, Ruskin, Darwin, Maxwell and Kelvin and of the foundation and early years of the Epidemiological Society of London; but an age in which aggregated masses of population in centres of civilisation were exposed to the free ravages of preventable disease. The third age was one of social reform, following upon the revolution effected by Chadwick, Shaftesbury, Farr, Simon, and Pasteur. coincident with the development of epidemiology, medical statistics, bacteriology, parasitology and public health, and with consequential reduction in mortality associated with privation and sanitary neglect: an age nevertheless of the great influenzas of the "nineties" and to be followed by those of the years 1915-25.

It is, of course, obvious, speaking again epidemiologically, that the first and third ages closely resemble one another and differ markedly from the second age. The resemblances and the contrasts are perhaps more apparent than real, but in so far as they may be held to exist, some part of the difference may be accounted for by the fact, that while in the first and third the people of this country were, on the whole, well nourished and, comparatively speaking, prosperous, in the second there was very great hardship and almost entire lack of social and humanitarian

effort. Apart, however, from this the pictures we have presented to us of the epidemic diseases of the three ages were largely coloured, so far as the first and third are concerned, by the scientific and artistic genius of two great epidemiologists, while the atmosphere of the second age was eminently unfavourable to any like accomplishment, for public health was struggling for its very existence, grappling with filth diseases, starvation and lack of nursing and institutional provision, and had no time to spare for giving expression to any higher forms of achievement. The spectre of hunger denominates the second age, much as that of the "associated organism" broods over the third, but just as the Chadwicks and Shaftesburys fought the former, so Creighton manfully countered, albeit not by a frontal attack but by a flanking movement, the attempt made by the "associated organism" to assume the title rôle in the drama of the third age.

And so it has chanced, as the outcome of the teaching of the *History of Epidemics in Britain*, that students of epidemics are to-day imbued with the feeling that analysis specialism and technique are being somewhat over-stressed; that synthesis and the broad world-view have been well-nigh ignored; and that a return to Sydenham and Hippocrates is urgently needed. Thinking in "light years" at one end of our scale of magnitudes, and in electrons and protons at the other end, has so filled us with wonder that we tend to overlook all that lies between the two extremes, and to forget what William James called the "really real," "the common-sense world and its duties," including its sanitary obligations. The same

writer warned us, however, in his *Humanism and Truth*, that " The fundamental fact about our experience is that it is a process of change, for the ' trower ' at any moment, truth, like the visible area round a man walking in a fog, or like what George Eliot calls ' the wall of dark seen by small fishes' eyes that pierce a span in the wide ocean,' is an objective field, which the next moment enlarges and of which it is the critic, and which then either suffers alteration or is continued unchanged. The critic sees both the first trower's truth and his own truth, compares them with each other and verifies or confutes." . . . " But the critic himself is only a trower."

Sydenham may have been right, therefore, when he concluded his discussion (Sch. Mon., I, paras 41 to 43) of that very question, which, as has been seen, so greatly intrigued nineteenth century epidemiologists (that of malignity in fevers and the teachings of reason and experience with regard thereto), by surmising that so difficult an argument might perchance only be successfully followed up by " beings in those brighter orbs, which are scattered over the infinite expanse of the universe, whose intelligences far exceed those of finite men." Indeed, speaking of the here and now, he says : " Man may so far have his intellectual faculties shaped by Nature, as to be enabled to perceive not what is absolute truth, but only that which is necessary for him to know and fitted to his nature."

This, however, he explains " applies to those whose medicine consists in vain speculations rather than in that solid experience which rests upon the basis of the senses."

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